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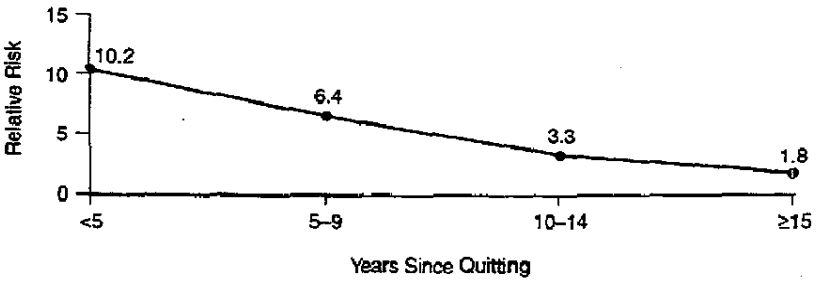
Figure 12-6 Relative risk of lung cancer death among former male smokers, relative to never smokers



NOTE: Data from Enstrom's (1999) prospective cohort study of U.S. male veterans, comparing 43,559 former smokers to 59,351 men who never smoked cigarettes.

SOURCE: Adapted from the Journal of Clinical Epidemiology, 52, Enstrom, J.E., Smoking cessation and mortality trends among two United States populations, 813-825, Copyright (1999), with permission from Elsevier Science.

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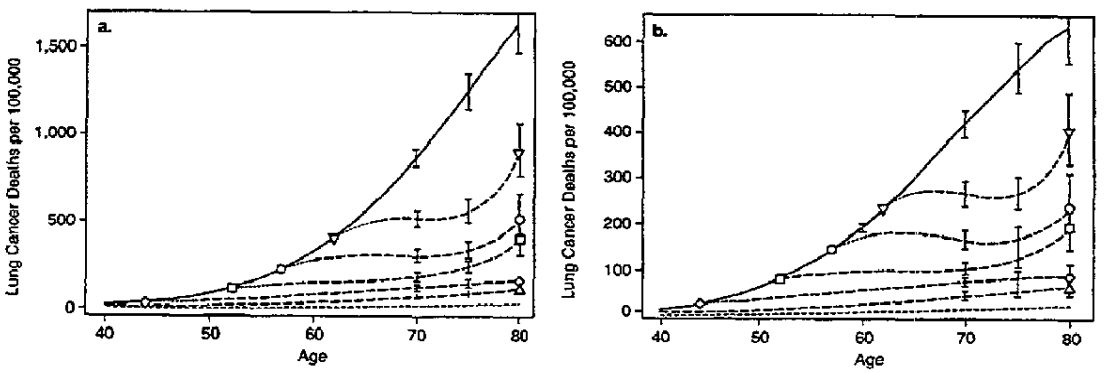
Figure 12-5 Lung cancer death rates of women and men



NOTE: Figure on the left: Model estimates of lung cancer death rates by age for female current, former, and never smokers, based on smokers who started at age 18.5 and smoked 22 cigarettes/day. Estimates are plotted for current smokers (solid line), never smokers (dotted line), and former smokers (dashed lines). The five age-at-quitting cohorts are distinguished by the following symbols on the graph at the age of quitting and also at age 80: Δ 30-39, ◊ 40-49, □ 50-54, O 55-59, ∇ 60-64.

Figure on the right: Model estimates of lung cancer death rates by age for male current, former and never smokers, based on smokers who started at age 17.5 and smoked 26 cigarettes/day. Estimates are plotted for current smokers (solid line), never smokers (dotted line), and former smokers (dashed lines). The five age-at-quitting cohorts are distinguished by the following symbols on the graph at the age of quitting and also at age 80: Δ 30-39, ◊ 40-49, □ 50-54, O 55-59, ∇ 60-64.

SOURCE: Data from Halpern et al. (1993): the American Cancer Society's Cancer Prevention Study II of 136,072 former smokers and 117,455 never smokers in comparison to 91,994 current smokers. Reprinted, with permission from Halpern et al. (1993). Copyright 1993 by the Journal of the National Cancer Institute.

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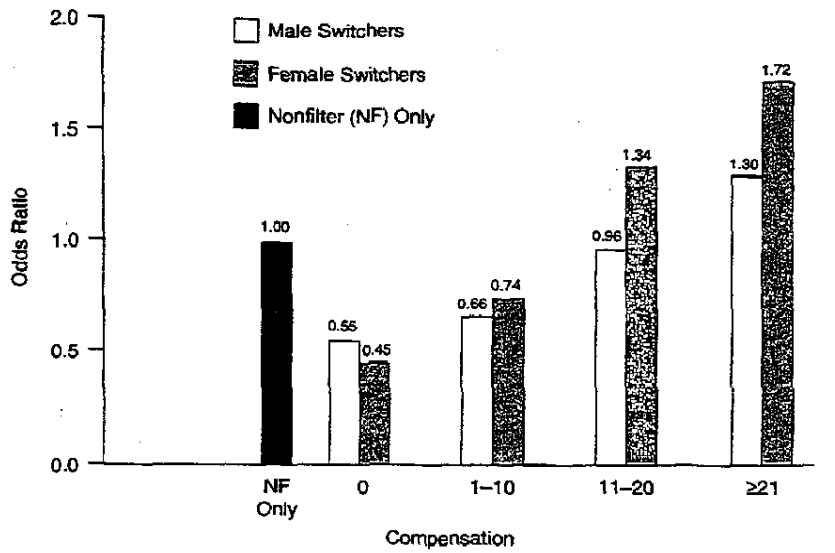
Figure 12-4 Risks among Switchers Relative to Nonfilter Only Smokers According to Difference Levels of Compensation



NOTE: Compensation is the increase in cigarettes per day after switching to filter cigarettes. Computed from the result of Augutine, Harris and Wynder study (1989) and the results of the study by Wynder and Kabat, 1988.

SOURCE: Reprinted from Augustine, A., Harris, R.E., and Wynder, E.L. Compensation as a risk factor for lung cancer in smokers who switch from non filter to filter cigarettes. American Journal of Public Health, 79: 188-191, Copyright 1989 by the American Public Health Association.

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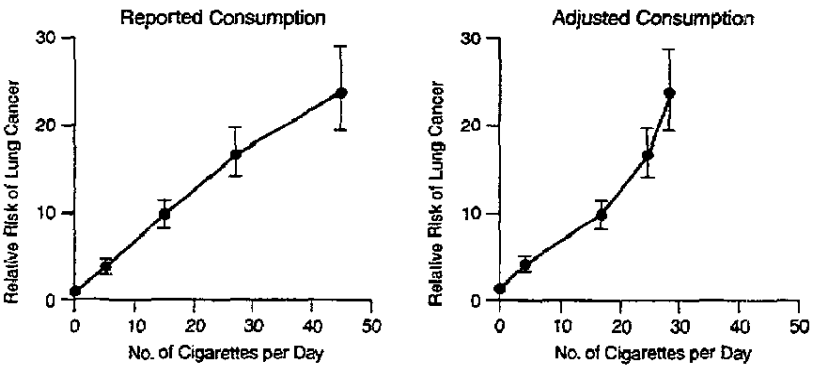
Figure 12-3 Relative risk of lung cancer verses number of cigarettes per day



NOTE: Estimates (with 95% confidence limits) from the U.S. veterans study (Kahn, 1996) of lung cancer mortality in current smokers relative to that in never smokers, according to reported cigarette consumption and adjusted cigarette consumption.

SOURCE: Reprinted from British Journal of Cancer, 75,11, Law, MR, Morris, JK, Watt, HC, Wald, NJ, The dose-response relationship between cigarette consumption, biochemical markers and risk of lung cancer, pg 1690-1693, 1997, by permission of the publisher Churchill Livingstone.

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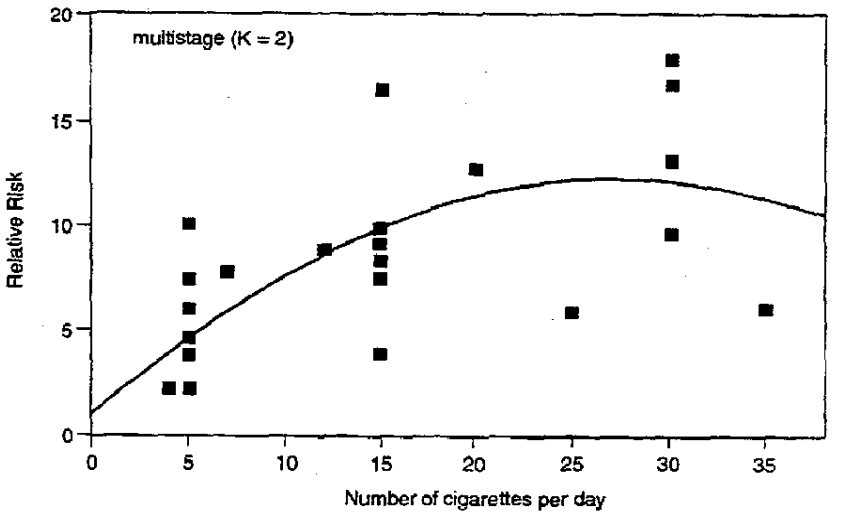
Figure 12-2 Relative Risk verses number of cigarettes per day.



SOURCE: Reprinted with permission from Puntoni et al. Mathematical modeling in risk/exposure assessment of tobacco related lung cancer. Carcinogenesis. 16:7, 1465-1471. 1995. Copyright (1995) Oxford University Press.

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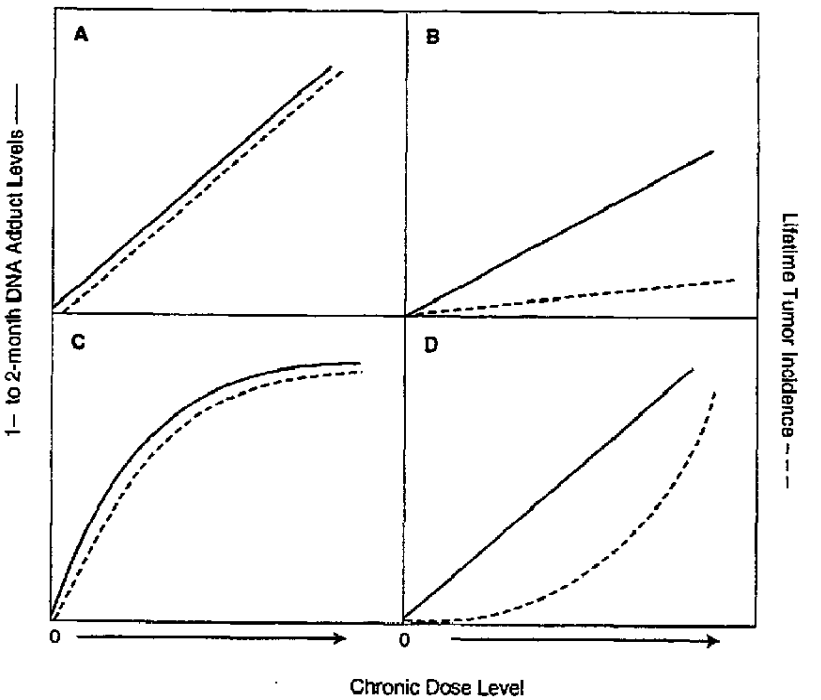
Figure 12-1 Lifetime tumor incidence



NOTE: "Schematic diagrams for the different patterns of lifetime tumor incidence (—) and DNA adducts at 4-8 weeks of administration (-), observed as a function of chronic carcinogen dosing" (Poirier and Beland, 1992)

SOURCE: Reprinted with permission from Poirier, M.C. and Beland, F.A. DNA adduct measurements and tumor incidence during chronic carcinogen exposure in animal models: Implications for DNA adduct-based human cancer risk assessment. Chem. Res. Toxicol, 5: 749-755, 1992. Copyright (1992) American Chemical Society.

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Source: https://www.industrydocuments.ucsf.edu/docs/zmlx0001

Table 12-5
Competing Risk Factors, Confounders, and Sources of Error in Tobacco–Cancer Associations

Problem	Examples
Competing risk factors and confounders	Type of tobacco product Variability in tobacco constituents Duration of smoking Dose estimates: daily vs. cumulative, packs per day, pack-years, etc Depth of inhalation Smoking behavior following a change in brand Tumor histology Age-related factors: starting, quitting, age at diagnosis ETS (duration, intensity, dose) Occupational exposure to carcinogens Air pollution Dietary factors: carcinogens, preventive substances Genetic predisposition Social and cultural factors Gender Race or ethnicity Education
Study design errors	Selection bias Recall bias Information bias (especially use of proxies in interviews) Poor choice of control subjects Inadequate matching, overmatching Lack of control for confounders
External factors	Publication bias

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Table 12-4
Examples of Variables Affecting the Success or Failure of PREPs

Variable	Questions
Effect on metabolic enzymes	1. Does a change in one or more tobacco constituent affect enzymatic induction or activity? 2. Does a change in enzymatic induction or activity result in a change in resultant DNA damage by the agent and, if so, by how much? 3. Does a change in enzymatic induction or activity result in a change in resultant DNA damage by other agents that are substrates in the same metabolic pathway and, if so, by how much? 4. Will people be affected differently because of interindividual differences in enzymatic induction or activity, and if so, what is the proportion of persons affected in a population (race, gender, age, etc.)? 5. Does a change in one or more tobacco constituent affect smoking behavior (e.g., absorption of nicotine, irritation, mucosal damage)?
Effect on DNA repair, cell-cycle control, and programmed cell death	1. Does a change in one or more tobacco constituents affect the induction or activity of DNA repair enzymes? 2. Does lowering exposure to one or more tobacco constituents result in less DNA damage from these constituents but also result in less time for cell-cycle arrest or less cell death, so that other carcinogens can cause more DNA damage or cell proliferation is enhanced? 3. Will individuals be affected differently because of interindividual differences in DNA repair, cell-cycle control, or programmed cell death, and if so, what is the proportion of persons affected in a population (race, gender, age, etc.)?
Effect on mutational spectra of gatekeeper and caretaker genes or tumor suppressor genes and oncogenes	1. Does a change in exposure to tobacco smoke carcinogens result in a change in the mutational spectra of one or several genes or in different RNA and protein expression profiles? 2. Do different levels of exposure result in different mutational spectra or RNA and protein expression profiles? 3. Does the mutational spectra or expression profile differ in persons who have changed their exposures compared to those who have not? 4. Does a tobacco constituent cause DNA damage through the formation of DNA adducts, free-radical damage, and/or gross chromosomal aberrations. (each of these mechanisms might affect the success of a harm reduction strategy and all might have to be considered)?

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Table 12-3
Scientific Methods for Carcinogenicity Testing

Method	Strengths	Limitations
In vitro cell culture models	Rapid, inexpensive. Can be used to study mechanisms in human cells. Can be used to prioritize other studies	Quantitative extrapolation to human risk cannot be done, so relevance to human experience is questionable
Laboratory animal models	Provides *in vivo* experience. Dosing protocols can be modified to assess changes in PREPs. Can be used to prioritize human studies. Can be used to develop and validate biomarkers. Transgenic mice available	Quantitative extrapolation to human risk cannot be done and so the relevance to human experience is questionable. Expensive
Human experimental models	Can provide data about short-term changes in exposure and resultant effects on biomarkers. Can assess complex mixture	Best used to assess effects on exposure rather than outcome (i.e., cancer). Expensive
Epidemiology	Provides direct experience and assesses tobacco use in the context of individual susceptibilities and complex exposures. Case-control studies provide rapid data. Prospective studies provide best evidence	Use of cancer end point means long latency periods and adverse effects on many people. Expensive

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Table 12-2
Causality Assessment[a]

Criteria	Comment
Strength of association	What is magnitude of risk?
Consistency	Are there repeated observations by multiple investigators in different populations?
Specificity	Is the effect specific or are there other known causes?
Temporality	Does exposure precede effect?
Biological gradient	Is there a dose–response relation?
Biological plausibility	Is the effect predictable?
Coherence	Is the effect consistent with other scientific data?
Analogy	Do similar agents act similarly?

[a]These criteria should serve as guidelines for assessment of PREPs. They rely on human studies (and are applicable to biomarker studies) and use experimental data to provide supportive evidence. The criteria were originally, published in the first Surgeon General's report[3] and later expanded by Sir Bradford Austin-Hill[4].

Source: https://www.industrydocuments.ucsf.edu/docs/zmlx0001

Table 12-1
List of Selected Tobacco Mutagens and Carcinogens[a]

Constituent Class	Phase	IARC Evaluation	Examples
N-Nitrosamines	Particulate	Sufficient in animals	Tobacco-specific nitrosamines (NNK, NNN), dimethylnitrosamine, diethylnitrosamine
Polycyclic aromatic hydrocarbons	Particulate	Probable in humans	Benzo[a]pyrene, benzo[a]anthracene, benzo[b]fluoranthene, 5-methylchrysene
Arylamines	Particulate	Sufficient in humans	4-Aminobiphenyl, 2-toluidine, 2-naphthylamine
Heterocyclic amines	Particulate	Probable in humans	2-Amino-3-methylimidazo[4,5-[b]quinolone (IQ)
Organic solvents	Vapor	Sufficient in humans	Benzene, methanol, toluene, styrene
Aldehydes	Vapor	Limited in humans	Acetaldehyde, formaldehyde
Volatile organic compounds	Vapor	Probable	1,3-Butadiene, isoprene
Inorganic compounds	Particulate	Sufficient in humans	Arsenic, nickel, chromium, polonium-210

aThis list is intended to provide a conceptual overview of the complexity of tobacco product exposures. It is not all inclusive, but is included to allow the reader to understand the number of considerations that must be made in assessing PREPs.

bInternational Agency for Research on Cancer: The classifications here refer to evaluations of the compound from any exposure, not just tobacco. Not all chemicals within the class are considered carcinogenic in humans. There is no consideration in this table of delivered dose or route of exposure.

Note: NNK = nicotine-derived nitroketone; NNN = N-nitrosonornicotine.

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that the delivered exposures from a PREP would be below the threshold, or at least this should be the goal of such a product. It is recognized that ETS data would suggest that the threshold, if any, is very low.

Do All New Products Need to Be Tested or Only Some That Would Serve as Indicators for Similar Products?

It would be efficient to have data that are representative of a class or type of product, where some screening tests could be used to ensure that a potential product fits within that class or type. However, data are needed to validate the assumption that representative products actually are representative.

Which Carcinogens Should Be Prioritized for Study, Given the Large Number Delivered By Tobacco Products?

While there is a need to study both individual carcinogens and tobacco exposure as a complex mixture, it will not be possible to evaluate all possible carcinogens. Thus, additional studies are needed that can compare the harmful effects of tobacco constituents, and models should be developed to prioritize their study. Further data are needed to achieve confidence that only a few key, but high-priority, carcinogens are sufficient to evaluate a PREP.

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it is recognized that such studies are expensive, additional costs will have to be added. These studies must follow subjects closely to document smoking behavior, use of all types of tobacco, modifying factors, and so forth. Smoking topography after switching brands should be assessed in at least a subset of individuals. Specimens should be collected at regular intervals, including buccal swabs, sputum, blood, and urine.

Given the long time for such cohorts to mature, emphasis might also be placed on establishing a complementary cohort of former smokers, because these persons will have the highest risk of recurrence in shorter periods of time. Biomarkers used in the former-smoker cohort that are found to be predictive of risk could then be used sooner in short-term epidemiological studies of PREPs.

Another group of subjects that might provide useful information about PREPs would be persons with surgically resectable cancers who will remain at high risk for developing new primary tumors or experience recurrence. These products might reduce the risk of either, so cohorts should be established to study these persons. Such studies would also provide valuable data for the worthiness of biomarkers.

SPECIAL ISSUES IN STUDY DESIGNS

Harm Reduction Compared to What Exposures?

Depending on study design, different exposure comparisons can be made, some of which are more applicable than others. For the development of biomarkers that are tested first in the laboratory setting (in vitro and in vivo animal studies), authentically synthesized tobacco carcinogens, or components of a reference cigarette (i.e., the tar fraction or cigarette smoke condensate from a Kentucky reference cigarette), would be preferable. Levels of exposure should be quantitated accurately so that the results can be interpreted in relation to the range of human exposures.

Experimental human studies in which the product is initially tested would optimally be compared to both reference cigarettes and separately to the smokers' usual cigarettes, where a range of smokers and cigarette types are used (i.e., low- and high-tar contents, menthol). The decreasing use of nonfilter cigarettes would make comparison to nonfilter cigarettes a low-priority consideration.

The comparison group for short- and long-term epidemiological studies would have to be usual cigarettes, because it is not feasible to ask persons to smoke reference cigarettes, which are not designed for appeal. Thus, these studies must carefully characterize smoking behavior, and a range of cigarette types and smoking behaviors must be included.

Harm Reduction Compared to What Risks?

It is clear that any PREP will likely bring some risk of cancer to the user. Comparison groups could be either never smokers, former, smokers or continuous smokers. Preferably, a PREP should reduce risk for the individual compared to the risk for that individual from the usual smoking behavior before switching to the PREP.

Is There a Threshold for CancerRisk and Does It Matter?

It is important to consider whether a threshold exists for risk of cancer from tobacco products. This is important for new smokers who might initiate smoking with a PREP. It is possible

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utility of biomarkers in relation to conventional tobacco products in order to evaluate difference among PREPs. For example, dose–response relationships can be established in ETS-exposed persons, former smokers, low- and high-level smokers, women and men, and different races and ethnic groups. Many biomarker studies classify persons only as current, former, and never smokers. However, this classification is inadequate to provide supporting evidence for use of these biomarkers in the assessment for PREPs. When a dose–response relationship does not exist, modifying factors have to be identified, and until then, the enthusiasm for a particular biomarker is lessened because its laboratory validity would be questioned.

Determine Whether There Are Susceptible Subpopulations That Might Benefit More or Less from a Potential Reduced-Exposure Product.

Data are sufficient to conclude that certain subpopulations are susceptible to tobacco-related harm, although there are insufficient data to conclude that any specific group carries different risks based on genetic susceptibilities, race, gender, et cetera. Human studies must consider different subpopulations and assess whether some who would benefit differently from a product.

Determine How Potential Reduced-Exposure Products Affect Human Exposure and Harm in Short-Term Human Clinical and Epidemiological Studies.

Clinical trials should be used. These studies would focus on biomarkers of exposure, biologically effective dose, and potential harm. Studies should be designed for smokers willing to try PREPs continuously for a specified period (e.g., 6 months). Accurate assessment of smoking behavior, such as cigarettes per day and smoking topography, and effects on biomarkers should be determined. Baseline specimens should be collected (sputum, buccal swabs, blood, and urine and, for some studies, possibly bronchoalveolar lavage or biopsies of internal organs) and then are followed frequently throughout the study. The choice of the biomarkers would depend on the criteria described in this report. The study of smoking behavior alone is insufficient because persons who increase use of a PREP might still have reduced exposure and harm. Biomarkers of internal exposure, biologically effective dose, and harm should be used.

In the context of harm reduction, developing fluorescent bronchoscopic techniques, coupled with molecular analysis, has the potential to identify smokers who have already sustained molecular damage and, depending on the type of damage, to indicate who might benefit most from harm reduction strategies.

The design of studies should allow for sufficient time to acclimate the smoker to the new PREP.

Determine How Potential Reduced-Exposure Products Affect Human Exposure and harm in Long-term Epidemiological Studies

These studies are the most problematic in early assessments of PREPs, because the latency period for cancers is too long to provide the needed results. Also, the technology for PREPs will likely change quickly, and an individual may use multiple types over a period of time. However, such studies should be started immediately in order to provide the definitive proof of success. Specifically, the emphasis in long-term epidemiological research should be on prospective cohort studies. Either existing cohorts should be modified, or new cohorts should be established. While

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reference cigarettes at different levels and times, and then change the exposure to simulate the PREP at different levels and times. This would better mimic the human scenario where persons who cannot quit will switch to such a product. These models would provide supportive evidence to identify the range of exposure situations that might provide the most benefits and whether some circumstances might result in absolutely no benefit.

There has been difficulty in developing animal models of tobacco-related cancers because animals breathe smoke differently than humans. Thus, additional efforts are needed in developing such models. Separately, genetically altered animals and cell lines can be used in the context of harm reduction in order to elucidate effects on different carcinogenic pathways.

It is important that laboratory experimental studies incorporate biomarkers along the range from exposure to potential harm and that molecular analysis of tumors be undertaken to provide data that would prioritize biomarker use in humans.

Development and Validation of Biomarkers for Cancer Risk Assessment

The following research agenda is intended to provide sufficient data to develop methods that can assess PREPs. It does not describe the methods for assessing a PREP.

Currently, the best biomarkers assess internal exposure, such as the use of exhaled carbon monoxide. There has been significant progress in developing biomarkers that measure the biologically effective dose, but these generally are not sufficiently sensitive or are too labor intensive to be used in large epidemiological studies. Thus, there are some biomarkers that can be used in smaller studies for assessing PREPs, such as the measurement of carcinogen–DNA adducts, where there are some data to support a relationship to cancer risk. There is less enthusiasm for markers where less specificity exists (i.e., chromosomal aberrations and sister chromatid exchanges).

Great emphasis is needed on developing more sensitive technologies for biomarkers of harm in normal-appearing tissues. For example, mutational load studies measuring p53 or K-ras mutations in normal tissues, LOH in sputum and urine cells, and so forth, have the potential to identify effects very early in the carcinogenic process. These biomarkers would have more importance than biomarkers that reflect mostly exposure.

It is clear that human studies and surrogate biomarkers will have the greatest applicability for assessing PREPs. However, although there are some data to show that the use of surrogate biomarkers can reflect the effects in a target organ, a need clearly exists for more studies of both existing and new biomarkers.

Biomarkers are needed that will assess the effects of specific carcinogens as well as complex mixtures. They also should consider exposures from particulate and gaseous phases, as well as oxidative damage.

Many new technologies are being used in studies of carcinogenesis and cancer diagnosis, such as proteomics and expression arrays. These technologies have the potential to provide important information about the use of a PREP and how the product would affect the carcinogenic process. Currently, the use of these technologies in cancer risk studies is embryonic, but such studies should begin for PREPs at the present time, notwithstanding the significant bioinformatic and data interpretation issues. If, for example, it is shown that enzyme induction in human lymphocytes is not substantially different between product types for key genetic pathways, then there would be less enthusiasm for the PREP.

Current and new biomarkers should be tested in different populations in order to understand the range of results and how they relate to different populations. It is important to understand the

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population or in large epidemiological studies is not yet available. In these studies, the characterization of smoking history and behavior is well validated for recent exposures but problematic for assessing lifetime exposure. Also, self-reported smoking history is insufficient to adequately assess risk in the context of PREP assessments, so biomarkers also are needed to assess exposure, biologically effective dose, and potential harm.

Currently, the best means of assessing PREPs and cancer risk is to focus on lung cancer because this is the most common cancer and so will provide studies with the greatest statistical power. However, data are sufficient to conclude that a risk exists that the widespread use of PREPs will shift the burden of cancer in the population from one type of cancer to another or from cancer to a different disease. Thus, a particular cancer type cannot be the sole indicator for the success of a PREP, and other cancers, diseases, and overall mortality must be evaluated.

There has been sufficient study of nicotine in the laboratory to conclude that it is unlikely to be a cancer-causing agent, although there are no studies of long-term human exposure. The consideration of nicotine as a carcinogenic agent is trivial compared to the risk from other tobacco constituents.

Smokeless tobacco products are associated with oral cavity cancers, and a dose–response relationship exists. However, the overall risk is lower than for cigarette smoking, and some products such as Swedish snus may have no increased risk. It may be considered that such products could be used as a PREP for persons addicted to nicotine, but these products must undergo testing as PREPs using the guidelines and research agenda contained herein.

Studying of the effects of PREPs on cancer risk from ETS is problematic because of the difficulties in measuring reductions in exposure. Also, while there is clearly an increased risk of lung cancer from ETS, the determination of changes in risk from the use of PREPs will require studies of large numbers of people, and smoking currently is prohibited in many places where ETS might have occurred.

RESEARCH AGENDA

Use of Laboratory Studies to Predict Effects of Potential Reduced-Exposure Products

Both in vitro cell culture and in vivo experimental animal studies are needed to identify the possible benefits of a PREP. It is beyond the scope of this report to recommend specific assays or animal models, but it is clear that no single model is sufficiently validated to be solely relied upon. Given that there is insufficient confidence in extrapolating results from laboratory studies to human risk, such studies should not be used alone to support a claim of possible or potential harm reduction. However, these studies are considered important because they can (1) reduce the enthusiasm for a product if there is an increased amount of harm compared to current marketed products; (2) can be used to identify mechanisms of carcinogenesis and how the PREP affects these mechanisms; and (3) identify unanticipated affects such as exposures to new or different carcinogens, different carcinogenic effects, or other unanticipated toxic effects.

The design of experimental studies that assess PREPs should be done in two ways. The first would focus on exposure to the components of the PREP as the sole exposure (i.e., tar fraction or a mixture of carcinogens that simulates yields from the product), preferably as a complex mixture. The main value of these studies would be not to identify the potential benefits of the product, but to assess its impact on persons who initiate smoking with this product and then stay with it. The second experimental design would be to use initial exposures that simulate those from

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This chapter has not reviewed potential cancer risks due to fibers released from cigarette filters or tobacco additives, because it is thought that the risk from these exposures is substantially less than the risk from tobacco smoke constituents. However, there are no existing data to prove this assumption. Importantly, as PREPs are developed that substantially reduce exposure to tobacco constituents, the role of fibers and additives in carcinogenesis might become more important. Thus, fiber and additive exposure should be considered when assessing PREPs.

There are some experimental models (e.g., in vitro cell culture and laboratory animal) that are useful for the assessment of PREPs. Although there are many reasonable models for assessing individual tobacco smoke products, better models are needed to assess exposures to complex mixtures. Such studies are not sufficient alone to support claims of potential harm reduction, and no claim of potential harm reduction should be allowed without adequate human clinical and epidemiological studies. These studies, however, are very important for (1) determining those products that are not likely to result in measurable harm reduction (e.g., if a product results in exposures that increase genotoxicity, there would be less enthusiasm for it, while the converse indicates only that further testing should be considered in humans) and so should not be tested in a human clinical study in anticipation and should not be introduced into the marketplace; (2) identifying unforeseen reactions (e.g., if a product reduces exposure but does not decrease tumors then there might be some constituent or combination of constituents that are either new or more important than those targeted for reduction in the product); (3) providing supportive evidence for the use of a particular bioassay in humans (e.g., if the same biomarker predicts cancer risk in experimental animals) and; (4) assessing the dose–response and the shape of the regression of risk for the PREP, although the data should be considered qualitative or semiquantitative and cannot be extrapolated directly to human smoking risk. Both in vitro cell culture and experimental animal studies should be used in assessing PREPs, where both can assess genotoxic and nongenotoxic end points, and chronic animal bioassays are needed to assess the end point of cancer risk. It is beyond the scope of this committee to recommend a specific panel of assays, but such a panel needs to be developed.. Also, these studies should assess changes both for specific carcinogens and for complex mixtures in which the latter should be mandatory.

There is sufficient evidence to conclude that human experimental studies and short-term clinical studies can indicate the harmful effects of tobacco products. Thus, such studies can be used to assess harm reduction. Through the use of biomarkers and surrogate indicators of cancer risk these studies can evaluate the manipulation of carcinogens and nicotine to reduce exposures and how these changes might affect smoking behavior, metabolic activation, enzymatic induction, conjugation, excretion, biologically effective doses (or their validated surrogates), and biomarkers of potential harm. Separately, these studies can assess differences in risk and provide evidence for modifying effects by genetic susceptibility, diet, life-style, occupation, and so forth. However, at the current time, there is no single biomarker or panel of biomarkers that can be considered adequate indicators of cancer risk by themselves because most have not been sufficiently validated. New technologies are offering new opportunities for biomarkers. Thus, experts will be needed to devise a panel of biomarkers that reflect different exposures, biologically effective doses, and pathways for potential harm.

It is clearly possible to assess the effects of PREPs on cancer as the ultimate outcome, and only such studies can provide definitive evidence for the success of a product. However, the long latency for cancer renders these studies infeasible for making such claims today or in the near future. Preneoplastic lesions or the identification of harmful effects in single cells might be used as indicators of the carcinogenetic pathway, but the technology to identify these in the general

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Nonetheless, reduction of exposures to tobacco smoke and tobacco products to the lowest possible levels may provide some benefit to individual users and to the general population. However, data are insufficient to conclude how much reduction in exposure would yield a measurable benefit for whom. Currently, methods that would reduce exposure to tobacco constituents to the greatest extent would likely provide the greatest benefit, but this remains to be proven.

A thoughtful approach to the assessment of PREPs and cancer risk requires consideration of many factors obtained from laboratory and human studies. Data are sufficient to conclude that a dose–response relationship exists for the use of tobacco products and cancer risk. In laboratory animals, the shape of the dose–response curves differs for different tobacco constituents, so that understanding the relationship to tobacco smoke as a complex mixture is difficult. In humans, there are sufficient data for different cancer types and tobacco products, although more data exist for tobacco smoking and lung cancer risk. These studies suggest a curvilinear response that increases most around 5 cigarettes per day and plateaus at 20 cigarettes per day. However, these studies do not consider actual smoking behavior and exposure, so the shape of this curve is not certain. There is some evidence to indicate that when internal exposure is considered through biomarkers, the shape of this curve follows a quadratic equation. Thus, data are insufficient to conclude a greater or lesser effect for a PREP at particular levels of smoking history. There are sufficient data to suggest that different populations have different dose–response relationships depending on gender, race, age, and ethnicity, although the actual risk levels have not been sufficiently defined to draw definitive conclusions about risks among groups. Based on these type of data and possible modifiers of cancer risk (e.g., genetic susceptibilities, diet, life style, occupation), it should be considered that PREPs might benefit people differently or not at all.

There is no evidence of a threshold for tobacco smoking and cancer risk. This conclusion is consistent with the knowledge that there are many carcinogens in tobacco smoke, the aggregate would work to increase risk at any level. Modeling for low-dose exposures indicates an increased risk with less than one cigarette per day. Thus, persons who initiate smoking with PREPs that contain tobacco would increase their risk for cancer, and there is unlikely to be a "safe" cigarette. Former smokers who resume smoking with such products would increase their risk further.

It is possible to conceptually extrapolate the regression of risk using PREPs and assume that the use of such products would bring a smoker to a risk equal to some lower level of lifetime exposure. However, it must be acknowledged that there are insufficient data to validate this assumption or indicate that a decrease in risk would be measurable for all or some smokers. There are insufficient data to indicate what the shape of the curve for regression of risk would look like.

Data are sufficient to conclude, with some caveats, that filtered cigarettes pose a lower risk than nonfilter cigarettes for lung cancer and possibly other cancers. The caveats are that this only occurs in persons who do not substantially increase the number of cigarettes they smoke per day or otherwise compensate for their smoking behavior due to lower delivered levels of nicotine. Also, these studies may be confounded by diet, life-style, or other characteristics of people who choose filtered cigarettes. The available data are suggestive, but not sufficient, to conclude that smokers of so-called low-tar cigarettes have a lower cancer risk compared to those who smoke higher tar cigarettes, with the same caveats as for filter smoking studies. However, there are insufficient data to assess the differences in risk for "ultralow", low and high-tar cigarettes that are filtered. This is because these cigarettes became available at a later date, so there was not enough latency in the general population to assess them until recently. There are insufficient data to adequately consider how risk changes from switching types of cigarettes.

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to date and have not been used frequently in studies of human cancer risk. Users of smokeless tobacco products have higher rates of endogenous nitrosation, as well (Nair et al., 1996). Other exposures that occur with the use of smokeless tobacco products include compounds that cause oxidative DNA damage (e.g., polyphenols), where the amount may be related to pH (Nair et al., 1996). Genetic susceptibilities, namely GSTM1 null, is associated with an increased risk of oral leukoplakia in India (Nair et al., 1999).

STUDIES OF NICOTINE MUTAGENICITY AND CARCINOGENICITY

Several studies have been conducted to determine if nicotine is genotoxic. Almost all studies that could be identified failed to find increased genotoxicity (Doolittle et al., 1991 and 1995; Yim and Hee, 1995; Trivedi et al., 1990 and 1993; Mizusaki et al., 1977), although there are conflicting data about the potential mutagenic activity of cotinine (Yim and Hee, 1995; Doolittle et al., 1995). Urine from rats exposed to nicotine was not mutagenic (Doolittle et al., 1991). The effects of coculture of nicotine and known genotoxic substances indicated an increased rate of mutations for some compounds and a decrease for others (Yim and Hee, 1995). Experimental animal studies using nicotine alone have not found that nicotine is carcinogenic to the exposed animal (Schuller et al., 1995; Martin et al., 1979) or to offspring of animals treated with nicotine (Martin et al., 1979). However, in experimental animals, nicotine can increase the frequency of tumors induced by other agents such as 7,12-dimethylbenz[a]anthracene (Chen and Squier, 1990), *N*-nitrosamines (Chen et al, 1994; Gurkalo and Volfson, 1982), hyperoxemia (Schuller et al., 1995), and *N*-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide (LaVoie et al., 1985), although there was no effect for other *N*-nitrosamines (Habs and Schmahl, 1984) and an antitumor effect in some cases (Zeller and Berger, 1989). Nicotine also is reported to reduce apoptosis in normal and transformed cells (Wright et al., 1993), but not in lung cancer cell lines (Maneckjee and Minna, 1994). Nicotine was shown not to induce growth of lung cancer cell lines (Pratesi et al., 1996). Long-term studies of persons treated with nicotine replacement therapy are not yet possible because of the short time during which such products have been available. Even though it is possible that nicotine might increase tumor occurrence due to other agents (e.g., have a promotional effect), the risk from co-treatment with nicotine replacement therapy in persons who continue to smoke is likely to be small compared to continued use of tobacco products at a higher rate. The amount of nicotine replaced is less than that available from cigarettes, and it does not have the spectrum of carcinogens present in tobacco products. Human studies have shown that the use of nicotine replacement products does not result in the formation of TSNAs such as NNK (Hecht et al., 1999), although no human liver microsomes in vitro increase the formation of NNK precursors (Hecht, 2000).

CONCLUSIONS

There are sufficient laboratory and human data to suggest that harm reduction might be an achievable goal for persons who cannot stop smoking, because there is evidence of decreasing risk for persons who quit smoking and there are differences in risk for persons who use different tobacco products and differ in the way they use them. Clearly, quitting smoking is the most effective method of reducing cancer risk, and the cancer risk to former smokers is the lowest-level risk that might occur from the use of any PREP. Importantly, it must be recognized that the use of any PREP will likely increase the risk of cancer at some level as long as there is exposure to tobacco carcinogens, in contrast to quitting, which stops exposure to all tobacco constituents.

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users of toombak had an extremely high RR for such tumors (Idris et al., 1998). Research from other parts of the world is far less complete, so it is not known at this point whether ethnic or cultural differences in susceptibility explain any of the geographic variability. In the U.S. are more conflicting. In some of these studies it is difficult to separate the effects of chewing tobacco from alcohol drinking because of the few nondrinkers. In the U.S., Winn and coworkers reported an 4.2-fold increased risk (95% CI=2.6, 6.7) in Southern white women who exclusively use snuff (Winn et al., 1981). In contrast, an analysis of the relationship between smokeless tobacco and cancer of the oral cavity in the National Mortality Followback Study did not detect increased risk (Sterling et al., 1992). In spite of the conflicting U.S. data, it can be concluded that snuff use in the U.S. also increases the risk of orophayrngeal cancers.

In Sweden, there is a very high rate of Swedish snuff (Snus) use. But, the use of snus in Sweden has generally not been associated with oral cavity cancer (Nilsson, 1998; Idris et al., 1998; Kresty et al., 1996; Schildt et al., 1998; Lewin et al., 1998). Snus is not fermented and so has a much lower level of N-nitrosamines(Nilsson, 1998) and has a lower genotoxic potential(Jansson, 1991), which might be related to the lack of increased risk.

The risks of other types of head and neck cancers from smokeless tobacco products have not been studied as extensively. Evidence for an elevated risk of nasal cancer in association with the use of snuff was reported in a case control study in North Carolina and Virginia (Brinton et al., 1984). Chewing tobacco was not associated with salivary gland cancer in a recent study of cases and controls in the United States (Muscat and Wynder, 1998).

Some authors have concluded that there is no association between smokeless tobacco and bladder cancer risk, but few studies have examined this association and the results are inconsistent (Burch et al., 1989). One of the few studies to report an increased risk of bladder cancer among snuff users was a very small study of 76 female cases and 254 controls, among whom 3 cases and 1 control reported snuff use (Kabat et al., 1986). In a larger case-control study of 332 white men with bladder cancer and 686 population-based controls, (Slattery et al., 1988) reported an increased but statistically nonsignificant risk among nonsmokers who used snuff or chewing tobacco. In another population-based study, (Burch et al., 1989) found no association of bladder cancer with chewing tobacco or snuff among men or women, but neither of these studies incorporated any exposure biomarkers and neither was specifically designed to test the hypothesis of smokeless tobacco risk.

The p53 gene is commonly mutated in cancers associated with smokeless tobacco products, and while some differences in the spectra have been reported for different regions of the world, no hotspots or patterns have been consistently shown compared to oral cavity cancers related to smoking (Saranath et al., 1999; Kannan, 1999, Ibrahim, 1999; Xu, 1998; Lazarus et al., 1996 a,b).

A major concern of health professionals is the presence of carcinogenic N-nitroso compounds in smokeless tobacco, which have been demonstrated to cause cancers of the mouth and lip, nasal cavity, esophagus, stomach, and lungs in laboratory animals. Hemoglobin adducts to these carcinogens are measurable in the blood of smokeless tobacco users (Carmella, et al., 1990), and, thus, may be useful biomarkers for measuring exposure levels among users. Urinary metabolites of TSNAs have been measured in persons using smokeless tobacco products, and higher levels were associated with oral leukoplakia, indicating greater use of the products (Kresty et al., 1996). Also, levels in snuff users were higher than those of chewing tobacco users. Hemoglobin-adduct levels have been found to be higher in snuff users than in nonusers (Carmella et al., 1990). However, such markers have been used only rarely in epidemiological studies

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In addition to the increased risk of lung cancer among cigar smokers in the Kaiser Permanente study (Iribarren et al., 1999), a synergistic effect of cigars and alcohol consumption was observed for oropharyngeal cancer, in which the RR for this cancer due to cigars and alcohol combined was much greater than for the independent effects of each substance alone.

Relatively few studies have examined the association of cigar smoking with bladder cancer. In their 20-year mortality follow-up study of 34,440 male British physicians who answered a questionnaire about smoking habits, (Doll and Peto, 1976) documented a significantly higher rate of bladder cancer deaths among men who smoked only pipes and cigars (14 per 100,000, age standardized) than among nonsmokers (9 per 100,000), compared to 19 per 100,000 among men who smoked only cigarettes. In the CPSII cohort of male cigar smokers who never smoked cigarettes Shapiro also found an association between cigar smoking and bladder cancer (Shapiro et al., 2000).

SMOKELESS TOBACCO PRODUCTS

Smokeless tobacco is consumed in a variety of different ways in various cultures around the world. Examples of smokeless tobacco products include chewing tobacco, dry snuff (used in the nasal cavity), wet snuff (a moist wad of tobacco, usually placed between the lips and gums), and nass (a mixture of tobacco, lime, ash, and cotton oil), with many local variations in Asia, the Middle East, and Africa. Large geographical differences in the prevalence of smokeless tobacco consumption are evident, with particularly high consumption in Scandinavia (where a popular form of snuff is known as snus), India, Southeast Asia, Sudan, and parts of the United States. Smokeless tobacco products from these different regions are produced differently and have different levels of carcinogens (Hoffmann and Djordjevic, 1997; Gupta et al., 1996). The popularity of smokeless tobacco increased sharply in the 1980s among young men in the United States, particularly among athletes and high school or college students (Christen, 1980). Data from the 1986–1987 National Survey of Oral Health in U.S. school children examined relationships between smokeless tobacco, alcohol, and the presence of oral soft-tissue lesions (Tomar et al., 1997). In the study sample of more than 17,000 children between the ages of 12 and 17, 1.5% had mouth lesions from smokeless tobacco. Factors associated with these lesions included male gender, white race, current snuff use, and current chewing tobacco use, with snuff having the highest OR (18.4). There was little evidence for risk modification by the use of alcohol.

Persistent use of snuff in the oral cavity causes a characteristic lesion, "snuff pouch keratosis," with a prevalence of 1.6 per 1,000 adults in a population-based study of 23,616 white American adults over age 35 (Bouquot, 1986). Almost 7% of the leukoplakias examined in that study were either carcinomas or severely dysplastic lesions. Early lesions can commonly be found in adolescent snuff users (Tomar et al., 1997). In India, chewing tobacco is associated with erythroplakia (Hashibe et al., 2000), and oral dysplasia (Kulasegaram et al., 1995). Stopping the use of smokeless tobacco results in the disappearance of oral leukoplakia (Martin et al., 1999).

Smokeless tobacco products are associated with cancers of the head and neck, depending on the type of tobacco used (Brinton et al., 1984; Jacob, III et al., 1999; Rao et al., 1994; Winn et al., 1981; Winn, 1997; Wynder et al.,1957)|, although not all studies are supportive of this conclusion. A large number of studies in India, including cohort, case-control, and intervention studies, support the association between oral cancer and smokeless tobacco, and these studies are consistent, strong, coherent, and temporally plausible (Idris et al., 1998; Wasnik et al.,1998; Sankaranarayanan et al., 1990; Nandakumar et al., 1990). Idris et al., compared oral cancer risks in the Sudan, where there an extremely high consumption of smokeless tobacco and found that

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geon General (Satcher, 1999). In that report, Dr. David Satcher notes that the popularity of cigar smoking has been especially pronounced among well-educated people. During this same period, cigarette sales fell by 3%, and taxes on cigarettes, but not cigars, were increased nationwide. Regular cigar smoking, however, is not a safe substitute for cigarette smoking. Cigar smoking is associated with increased risks of oral, esophageal, laryngeal, and lung cancers and with coronary heart disease and chronic obstructive pulmonary disease. Accordingly, the Surgeon General warned that cigars should not be viewed by the public as a safe and lower-cost alternative to cigarette smoking and called for warning labels, increased public awareness, and youth education efforts about the risks of cigars.

One of the limitations in studying the effects of cigar smoking on lung cancer risk is the relative rarity of cigar smokers compared to cigarette smokers in the population, and the fact that some smokers tend to mix tobacco products presents further challenges to disentangling potential cigar-related effects from cigarette-related effects. Many case-control studies have not had sufficient numbers of cigar smokers to analyze the risks.

(Boffeta et al., 1999) Pooled data from seven large case-control studies in Germany, Italy, and Sweden. All except one of the studies used population-based controls in comparison to lung cancer cases, and proxies provided interview data for deceased cases. In Europe, small cigars (cigarillos) are popular, and these were analyzed separately from large cigars. Relative to lifelong nonsmokers, age-and study-adjusted analyses revealed that the risk of lung cancer was elevated among people who smoked only large cigars (OR = 5.6, 95% CI = 2.9, 10.6), and among those who smoked only cigarillos (OR = 12.7, 95% CI = 6.9, -23.7). The OR was 14.9 (95% CI = 12.3, -18.1) among exclusive cigarette smokers and 12.7 (95% CI = 10.3, -15.6) among smokers of mixed tobacco products. The dose–response relationship between cigar and cigarillo use and lung cancer risk was strong, whether analyzed by years of use (P = .0003 for trend), grams of tobacco per day (P = .01), or age at smoking initiation (P = .002).

The above risk ratios have been described independently and consistently in several other European studies, among them the Seven Areas Study in which (Lubin et al., 1984) reported an OR of 5.6 for large cigars and 11.6 for cigarettes. (Boffeta et al., 1999) suggested that the lower OR for cigars compared to cigarettes is not due to lower carcinogenic potential, but rather to lower cumulative lifelong consumption and later age at smoking initiation of cigars.

In comparison, a review of 14 American studies (Shanks and Burns, 1998) documented cigar-associated lung cancer risks as lower than those of cigarette users, but the risk estimates for cigars were only modestly elevated. Reasons for the risk-level discrepancies in European and American case-control studies of lung cancer and cigar smoking may include several factors: (1) Americans overall prefer large types of cigars, whereas Europeans favor cigarillos; (2) differences in the constituents of the products; (3) differences in inhalation and other behavioral parameters of smoking; (4) consistent misclassification of cigar smokers in American studies; (5) differences in the proportions of histological types of lung tumors; and (6) differences in age at taking up smoking. Clearly, more research is needed to resolve these issues.

Several large, prospective studies of cigar smokers have documented significantly increased risks of lung cancer during long periods of follow-up compared to nonusers of tobacco. For example, (Iribarren et al., 1999) followed a cohort of nearly 18,000 men enrolled in the Kaiser Permanente Health Plan, among whom 1,546 cigar smokers were studied for several decades. The RR for lung cancer, adjusted for age and other covariates, was 2.14 (95% CI = 1.12, -4.11). Shapiro and coworkers (Shapiro et al., 2000) studied the risk of lung cancer in cigar smokers who never used cigarettes. These individuals had an RR of 5.1 (95% CI = 4.0, 6.6).

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critical question when the RR is weak (i.e., <1.5) because the impact of statistical confounding can obscure the true level of risk in such situations. Although Lee concluded that it was impossible to determine that ETS exposure is linked to increased lung cancer risk because of potential biases, his own estimates examining the available literature in many different ways still lead to the conclusion of an association. For example, providing a summary estimate where dose–response data are available, thereby reducing some biases, a risk estimate of 1.24 (95% CI = 1.15, 1.35) was found. In that review, Lee reported evidence for confounding by a number of factors: (1) continent—with RRs in European studies exceeding those in Asia and the United States; (2) publication date—with earlier publications (1981–1989) tending to report higher risks than more recent publications; (3) histology—with RRs in studies that confirmed primary lung tumors tending to be greater than those using unconfirmed cases; (4) dose—response data, with studies providing such data more likely to detect significant effects of ETS than those that did not provide such data; (5) type of control—with RRs from studies using disease controls tending to be higher than studies using healthy controls; (6) assessment of confounders, which tends to reduce RRs compared to studies that did not adjust for confounders; and (7) age matching, which tends to produce lower risk estimates than unmatched studies. Additionally, Lee noted that many studies of ETS did not match on marital status, most only adjusted for one or two confounders (leaving a high potential for uncontrolled confounding), and most considered only a single source of ETS rather than taking multiple sources into account. Still another factor that should be mentioned is the method of interviewing proxies when a case is deceased, which tends to introduce information bias or at the least nondifferential errors.

Considering other sources of bias, one study examined recall bias and misclassification of smoking status by examining smoking histories reported by spouses and concluded that there was no recall bias (Nyberg, 1998). Examining studies that use cotinine to classify ETS exposures, Tweedie and Mengersen used a meta-analysis approach and concluded that ETS risk was 1.17 (95% CI = 1.06, 1.28) (Tweedie and Mengersen, 1992).

Epidemiological studies of ETS risks that incorporate cotinine measurements are able to validate the classification of subjects according to self-reported levels of ETS. For studies lacking this biomarker, a major issue in estimating the cancer risks associated with ETS is the potential misclassification of former smokers as nonsmokers, which would tend to inflate the true risk ratios. A study of two large cohorts in Sweden, one involving twins and the other of randomly surveyed adults in the population, estimated that about 5% of former smokers were misclassified as never smokers, with roughly equal proportions in men and women. The RR for lung cancer among misclassified men was 1.9 (95% CI = 0.5, -9.1), indicating no statistical association, compared to 4.5 for correctly classified former smokers and 13.3 for current smokers (Nyberg et al., 1997). The authors of that study concluded that misclassification occurs mainly among very light smokers and long-term ex-smokers. Future studies of ETS should use cotinine measurements to estimate the impacts of such classification errors.

It was not easy to show that ETS affects biomarkers of cancer risk (Scherer et al., 1992). However, improved methodologies now show that ETS-exposed persons have elevated levels of TSNA metabolites in their urine.[9] Other studies have reported an increase of aryl amine-related adducts (Maclure et al., 1989).

CIGAR SMOKING

Cigar smoking has increased tremendously in the United States in recent years, with sales increasing as much as 50% between 1993 and 1998 according to a recent commentary by the Sur-

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ENVIRONMENTAL TOBACCO SMOKE

Environmental tobacco smoke, also termed passive smoking or exposure to secondhand smoke, has been estimated to cause 2,600 to 7,400 lung cancer deaths per year among nonsmokers in the United States, according to a review of 9 studies of lung cancer mortality (Repace and Lowrey, 1990). Animal models have established the carcinogenicity of ETS (Witschi, 1997a; Witschi et al., 1997b) Despite widespread workplace restrictions on smoking and public education about the dangers of secondhand smoke to adults and children, millions of people continue to be exposed to ETS. Data from NHANES III, a representative sample of the health of the U.S. population, show that 43% of children were living in a house with one or more smokers, and 37% of adult nonsmokers reported either having one or more smokers living in the same house or being exposed to tobacco smoke in the workplace (Pirkle et al., 1996). Also, 88% of nonsmokers tested positive for serum cotinine. Workplace bans on smoking have been highly effective in reducing ETS, but lesser workplace restrictions have been shown to be much less effective and many nonsmokers continue to be exposed to ETS on the job (Hammond, 1999). Any future strategies to reduce the harm from smoked tobacco products must therefore consider the potential effects on persons exposed to ETS.

Many studies have focused on indirect markers of ETS exposure, such as the presence in the home of a spouse who smokes or the number of years exposed to ETS. Direct measurements of ETS biomarkers (e.g. cotinine in urine, blood, or saliva), have also been widely implemented. Cotinine, the direct metabolic breakdown product of nicotine, with a biological half-life of 20 hours in urine, has been shown to meet all of the criteria for a highly sensitive and specific marker of ETS (Benowitz, 1999). Cotinine levels in children are highly correlated with adult cotinine levels (Crawford et al., 1994) and with the number of adult smokers in the household and the number of cigarettes smoked by the adults (Bono et al., 1996). ETS results in increased adduct levels and carcinogen metabolites in humans (Maclure, 1989; Hecht, 1993; Vineis, 1993).

The initial evidence linking ETS with increased risks of lung cancer came from studies in Japan and other countries in which smoking among women is rare. The conclusion that ETS is a cause of lung cancer has been opined by several reviewers and persons conducting meta-analysis (Brownson et al., 1998 and 1997; Zeise et al., 1997). In many studies, the risk of lung cancer among nonsmoking women was evaluated in relation to the presence or absence of a husband who smokes. For example, (Fontham et. al., 1991) reported an OR of 1.5 for the association of lung cancer among lifetime nonsmoking women who lived with a spouse who smoked. In that study, there was no significant association with childhood ETS exposures. On the other hand, (Janerich et al., 1990) found no association with ETS exposure in adulthood, but an OR of 2.0 was found for high levels of household tobacco smoke in childhood. (Stockwell et al., 1992) compared 210 women with lung cancer who were lifetime nonsmokers with 301 controls assembled by random-digit dialing. The maximum effect detected was an OR of 2.4 (95% CI = 1.1, - 5.3) for more than 40 smoke-years of exposure (with $p = 0.004$ for trend). Childhood ETS exposures yielded ORs and trends very similar to those associated with adult ETS exposures. Numerous other studies support the conclusion that ETS exposure increases lung cancer risk (Hirayama, 1981; Brownson et al., 1998 and 1992; Stockwell et al., 1992; Tweedie and Mengersen, 1992; Darby and Pike, 1988).

A recent review by Lee of 44 ETS studies revealed that the RR of lung cancer among nonsmokers is between 1.16 and 1.24 for women having a husband who smokes, relative to nonsmokers whose husbands are also nonsmokers (Lee, 1998). Furthermore, this report assessed the impact of a number of potential covariates on the magnitude of the ETS association. This is a

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tion may induce p53 mutations, which in turn are involved in early steps of bladder carcinogenesis.

Aromatic amines are metabolically conjugated in the liver, excreted in the urine, and then metabolically activated in the bladder (Ross et al., 1996). DNA adducts have been described in the bladder epithelium of smokers and nonsmokers (Phillips and Hewer, 1993; Talaska et al., 1991). Although most of the DNA binding appears not to be smoking related, the levels of several specific adducts were found to be significantly elevated in DNA samples of current smokers, as opposed to never smokers or former smokers (5 years' abstinence). Detection of DNA adducts in cells in voided urine may be a noninvasive method for following subjects at increased risk (Talaska et al., 1993).

Studies have shown that smoking-related bladder cancer risk and survival increases with genetic susceptibilities for carcinogen metabolism and detoxification, mostly for GSTM1 and NAT2 (Okkels, 1992 and 1996; Katoh, 1995; Brockmoller et al., 1998 and 1996; Rebbeck, 1997; Katoh et al., 1998; Mommsen and Aagaard, 1986; Risch et al., 1995; Taylor et al., 1995; Bell et al., 1992). Persons with low activity of CYP3A were associated with higher p53 overexpression (Romkes et al., 1996). Only one study relates adduct levels to bladder cancer risk (Peluso et al., 1998), but because this was a case-control study, conclusions are limited. However, in a small group of patients *(N = 45)*, adduct levels were not related to p53 mutations in tumors, but this was not a prospective study (Martone et al., 1998).

In summary, the bladder is a remote site from carcinogen entry into the body. Because urine is easily accessible, there are unique opportunities to study the effects of PREPs on bladder epithelial cells, especially in the context of genetic susceptibilities. However, although there are data showing that some cigarettes produce lesser risks if they are filtered, there also are data to indicate that changing to lower-tar cigarettes is not beneficial. If these data can be replicated, then it is suggested that the potential benefits of PREPs will be difficult to measure. In persons with occupational exposures that increase risk of bladder cancer, the potential benefit of a PREP may be minimized.

ENDOMETRIAL CANCER

Several studies have found that cigarette smoking reduces the risk of endometrial cancer. Although there are no prospective studies, case-control studies are fairly consistent. For example, in a study by Lesko and coworkers, 510 women with endometrial cancer were compared with 727 women with other types of cancers; the RR for current smokers was 0.7 (95% CI = 0.5, 1.0), and a dose–response effect was noted (Lesko et al., 1985). The effect occurred predominantly in postmenopausal women. A study by Brinton and coworkers reported a RR of 0.6 (95% CI = 0.4, -0.9) in postmenopausal women, where current smokers had the lowest risk and former smokers had an intermediate risk (Brinton et al., 1993). Other studies are in agreement (Levi et al., 1987; Austin et al., 1993; Parazzini et al., 1995). This reduced risk is thought to be related to an effect of smoking on circulating estrogens and androgens, which are also affected by other factors such as increased weight (Austin et al., 1993). In a study of postmenopausal women, smoking was associated with a decreased risk in women who did and did not use estrogens, although the effect was greater in the former (Franks et al., 1987). Smoking was found to modify the association of increased weight and endometrial cancer, where there was no increased risk in smokers (Parazzini et al., 1995; Lawrence et al., 1987). No studies have reported data for the effects by cigarette type.

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cigarettes per day for 20 years was 2.9 for men and women in England and Wales (Stevens and Moolgavkar, 1979). Another important bladder cancer risk factor is occupational exposure to aromatic amines (Ross et al., 1996). Several studies report an interactive effect for increasing risk in such workers who smoke (Vineis et al., 1984; D'Avanzo et al., 1990; Vineis and Martone, 1996). For bladder cancer, then, PREPs for individuals must be considered in the context of the workplace.

A recent study focused on the relationship of smoking and the progression of superficial cancers (Fleshner et al., 1999). Continued smokers experience worse disease-associated outcomes than patients who quit smoking. The authors recommended that smoking cessation be employed as a tertiary prevention strategy for patients with superficial cancers.

Cigarette type can influence bladder cancer risk. There is a higher risk with black tobacco than with blond tobacco (Vineis et al., 1984; D'Avanzo et al., 1990; Vineis and Martone, 1996). Filter-tip cigarettes pose a lower risk (Vineis, 1983; Vineis et al., 1984), although this finding is not consistent (Burch et al., 1989). Importantly, only one study which the committee is aware collected data for switching from nonfilter to filter cigarettes conflict (Hartge, 1987; Burch et al., 1989). In this, there was a small benefit from switching, but this was more pronounced in persons who had switched more than 15 years prior to diagnosis, and there was no benefit when the data were examined for persons aged 21–64 years rather than 21–84 years (Hartge, 1987; Anwar et al., 1993). The data were adjusted for smoking duration and cigarettes per day, but compensation was not specifically queried. Moreover, although there was a decreased risk with filtered cigarettes, there was no difference between smokers who smoked only nonfiltered cigarettes and those who switched. Increasing depth of inhalation has been reported as a separate risk factor (Slattery et al., 1988; Burch et al., 1989).

(Doll and Peto, 1976) found that among male British physicians followed for 20 years since an initial survey of smoking habits, the annual age-adjusted rate of bladder cancer deaths was 11 per 100,000 among men who had quit smoking, compared to 9 among nonsmokers and 19 among men who smoked cigarettes exclusively. Benefits from giving up cigarette smoking were quantified in a large cohort study of Kaiser Permanente Medical Care Program members in the United States (Habel et al., 1998). among current smokers, former smokers, and never smokers the standardized bladder cancer incidence ratios were 0.56, 0.68, and 1.04, respectively.

Chromosome 9 alterations and TP53 mutations are among the most frequent events in bladder cancer. Several studies have explored the relationships between epidemiological risk factors (especially smoking) and these genetic alterations. Elevated odds ratios were found for chromosome 9 alterations in smokers compared to nonsmokers (OR = 4.2, 95% CI = 1.02, -17.0) after controlling for age, sex, race, occupational history, and stage of disease. For chromosome 9 alterations, the OR was 3.6 for those smoking 20 cigarettes per day (Zhang et al., 1997). One study reported an association of smoking status and p53 mutations (Zhang et al., 1994), although others disagree (Spruks, 1993; Xu et al., 1997). For p53, a significant association between the number of cigarettes smoked per day and p53 protein nuclear overexpression was found ($p = .02$) (Zhang et al., 1994). The odds ratios were 2.3 for those smoking 1–2 packs per day and 8.4 for those smoking more than 2 packs a day. In addition, a distinct mutational spectrum for the p53 tumor suppressor gene in bladder carcinomas was reported in patients with known exposures to cigarette smoke (Xu, 1997; Spruck et al., 1993).The P53 mutations in bladder cancers from workers with aromatic amine exposure have the same spectra (Djordjevic et al., 2000). These data support the hypothesis that certain carcinogens derived from cigarette smoking and occupa-

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for tobacco and alcohol users was higher than for either of these exposures alone (Brennan et al., 1995).

The above information suggests that assessments for oropharyngeal and lung cancer risk related to the use of potential inhaled (i.e., tobacco smoke) PREPs are similar. It can be inferred that a suggested benefit for lung cancer would also benefit oropharyngeal cancer. However, these studies cannot imply that the quantitative benefits might be similar or even measurable in persons who continue to drink alcoholic beverages because of the synergistic effect of tobacco smoking and alcohol. The study of persons with oropharyngeal neoplasms provides some opportunities because of the accessibility of tissue and the occurrence of preneoplastic lesions.

BLADDER CANCER

More than 53,000 cases of bladder cancer will occur in the United States in the year 2000, and approximately 12,000 persons will eventually die from this disease (Greenlee et al., 2000). The male–female ratio is about 2.6:1. About 70% of bladder cancers are superficial at the time of presentation (i.e., confined to the mucosa or submucosa), while the rest are deeply invasive (Soloway and Perito, 1992). Most bladder cancers in this country are transitional cell carcinomas, arising from the normal transitional epithelium after multistage progression (hyperplasia, dysplasia, carcinoma in situ, superficial invasion). However, in some parts of the world such as Egypt, where schistosome infection of the bladder is common, squamous cell carcinomas are associated with chronic inflammation and squamous metaplastic changes. The chemicals most commonly implicated in bladder cancer in humans are aromatic amines, although other compounds such as PAHs might also play a role (Vineis and Pirastu, 1997; Ross et al., 1996).

Patients with cancer of the urinary bladder often present with metachronous tumors, appearing at different times and at different sites in the bladder. This observation has been attributed to a "field defect" in the bladder that allows the independent transformation of epithelial cells at a number of sites. Analyses of clonality indicate that a number of bladder tumors can arise from the uncontrolled spread of a single transformed clonal population (Sidransky et al., 1992). The molecular pathology and development of bladder cancer have been reviewed recently (Rao et al., 1999). As with other cancers, many molecular changes have been described in bladder cancers, including p53 gene mutations, p16 and retinoblastoma gene silencing, LOH at various chromosomal regions, aberrant methylation, and the presence of microsatellite alterations.

Many studies have shown a dose–response effect of smoking on bladder cancer risk in both men and women (Vineis, 1983; Hutge, 1987; Vineis et al., 1984; Slattery et al., 1988). A recent report summarized a combined analysis of 11 case-control studies (Brennan et al., 2000). The authors found a linear increasing risk of bladder cancer with increasing duration of smoking, ranging from an OR of 1.96 after 20 years of smoking (95% CI = 1.48, -2.61) to 5.57 after 60 years (95% CI, = 4.18, -7.44). A dose–response relationship was observed between number of cigarettes smoked per day and bladder cancer up to a limit of 15–20 cigarettes per day (OR = 4.50, 95%CI = 3.81, -5. 33), after which no increased risk was observed. An immediate decrease in risk of bladder cancer was observed for those who gave up smoking. This decrease amounted to more than 30% after 1–4 years, (OR = 0.65;, 95% CI = 0. 53, -0.79) and was more than 60% after 25 years of cessation (OR = 0.37; 95% CI = 0. 30, -0.45). However, even after 25 years, the decrease in risk did not reach the level of the never smokers (OR = 0.20; (95% CI = 0.17, -0.24). The proportion of bladder cancer cases attributable to ever smoking was 0.66 (95% CI = 0.61, -0.70) for all men and 0.73 (95% CI = 0.66, -0.79) for men younger than 60. These estimates are higher than previously calculated. Using a modeling approach to mortality data, the RR for 20

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studies are available, there are no differences in risk for similar levels of smoking in Caucasian Americans compared to African Americans (Blot et al., 1988; Day et al., 1993), although one study suggested that African Americans were at a lower risk, but there was no breakdown by smoking and drinking categories.

Smoking cessation changes the risk of oropharyngeal cancers. Cancer of the larynx has been found to be markedly less likely among ex-smokers than among current cigarette smokers.[3] In a relatively large case-control study in Brazil (Schlecht et al., 1999), 784 cases of cancer of the mouth, pharynx, and larynx were compared to 1,578 noncancer controls, compared to never smokers, the ex-smokers of >20 years had an OR = 2.0 (95% CI 1.0, -3.8) for all types combined, lower risks for mouth (OR = 1.6) and pharyngeal cancer (OR = 1.5), and a high risk for laryngeal cancer (OR = 3.6). The benefits of quitting were greatest for cigarettes and lesser for cigars and pipes.

Excellent reviews have been published of the molecular changes present in oropharyngeal cancer (Mao and El-Nagger, 1999; Sidransky, 1997). Many of the molecular changes in smoking-related upper aerodigestive tract tumors, including lung and oropharyngeal cancers, are similar and commence during multistage pathogenesis (Mao and El-Nagger, 1999; Sidransky, 1997). Changes include frequent losses at chromosome arms 3p, 9p, 17p, 5q; and 8p, aneuploidy, p53 gene mutations and expression abnormalities of the TGF-β signaling pathway, activation of telomerase, downregulation of RAR-α, and inactivation of the p16 gene (Brennan et al., 1995; Field et al., 1995; Izzo et al., 1998; Picard et al., 1999). Deregulation of the cell cycle is related to the degree of tobacco exposure (Davidson et al., 1996; Gallo et al., 1995).

Oropharyngeal tissues clearly have the capacity to metabolically activate tobacco smoke carcinogens and cause DNA damage (Mathias, 1998; Liu, 1993; Degawa, 1994) (Badawi et al., 1996; Kabat et al., 1991). Among the highest levels of CYP1A1 have been reported in these tissues compared to others (Kabat et al., 1991). NAT1, but not NAT2, activity is present, and there is some evidence that CYP2C plays an important role in these tissues. Aromatic DNA and 4-ABP adducts have been detected in laryngeal tissues; these were higher in smokers than in nonsmokers Flamini et al., 1998; Szyfter et al., 1994). Adduct levels in oral mucosa are correlated with biopsy levels indicating that mucosa can be used as a surrogate marker (Stone, 1995).

Several studies have indicated an increased risk of oropharyngeal cancers in those who have a heritable trait demonstrated by genetic polymorphisms, although which markers play the greatest role is not yet known (Morita,1999; Henning, 1999; Trizna, 1995; Sturgis, 1999) (Sumida et al., 1998; Helbock et al., 1998; Rebbeck, 1997; Cullen et al., 1997; LeVois, 1997), and there is some evidence for a greater effect in persons with lower levels of smoking (Jourenkova et al., 1998). In one study, heritable traits in carcinogen metabolism increased the frequency of p53 mutations (Lazarus et al., 1998). When cultured lymphocytes are exposed to mutagens and resultant chromosomal breaks are counted, there is a greater mutagen sensitivity in cases, especially smokers (Cheng et al., 1998; Cloos et al., 1996; Schantz et al., 1997; Spitz et al., 1993). This trait also predicts the risk of secondary cancers in persons with oropharyngeal cancer (Spitz et al., 1994). There are some data to suggest that smoking might increase mutagen sensitivity, so there might be an inductive effect in this assay (Wang et al., 2000).

The mutational spectrum of p53 in oropharyngeal cancers is similar to that in lung (Liloglou et al., 1997), although some studies disagree (Olshan et al., 1997). Mutations occur more commonly in smokers than nonsmokers (Lazarus et al., 1996b; Brennan et al., 1995; Liloglou et al., 1997; Field et al., 1994). In a study by Brennan and coworkers, the frequency of p53 mutations

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The data supports the conclusion that after about 20 years of quitting, the risk reduction plateaus and remains slightly above never smokers. Thus, it is unlikely that a PREP would achieve a greater level of risk reduction than the level at 20 years, and at any time point before that, the risk is likely to be greater than that of someone who quit.

OROPHARYNGEAL CANCERS

Oropharyngeal cancers include cancers arising in the oral cavity, tongue, pharynx, and larynx. Almost all are squamous cell carcinomas. Their incidence is about 40,000 cases annually, of which about 12,000 will eventually die from the disease (Greenlee et al., 2000). There is a male–female ratio of about 2:1.

Preneoplastic lesions, which include keratosis, dysplasia, carcinoma in situ, and microinvasive cancer, are considered a sequential continuum(Gillis et al., 1983). Keratosis is the most common oral lesion, occurring as white (leukoplakia) or red (erythroplakia) patches, and is present in 1-10% of adults (Mao and El-Naggar, 1999). Some molecular evidence exists that premalignant lesions are the direct precursors of invasive lesions (Califano et al., 2000). Cessation of smoking does not remove the potential for progression of the disease and all patients must be followed indefinitely (Gillis et al., 1983).

The major risk factors for oropharyngeal cancers are tobacco and alcohol use. The role of smokeless tobacco is discussed below. There is a dose–response for both smoking and alcohol use; together the two agents act synergistically (Barasch, 1993; Ahrens, 1991;Keller and Terris, 1965; Blot et al., 1988; Sanderson et al., 1997; Macfarlane et al., 1995; Schildt et al., 1998; Talamini et al., 1998; Hayes et al., 1999; Takezaki et al., 1996; Mashberg et al., 1993; La Vecchia et al., 1990; Muscat et al., 1996; Iribarren et al., 1999; Lewin et al., 1998; Schlecht et al., 1999). The attributable risk for alcohol and/or tobacco use is about 75–80% for males and 52–61% for females (Blot et al., 1988; Hayes et al., 1999). There is some evidence for a weak familial association in smokers (Goldstein et al., 1994). Some studies suggest that tobacco consumption is more likely than alcohol consumption to cause precursor lesions (Jaber et al., 1999; Kulasegaram et al., 1995) and cancer (Macfarlane et al., 1995; Elwood et al., 1984). An other study reported the converse in women (Schildt et al., 1998), although this was a small study of Swedish women who may have been snuff users (see section on Smokeless Tobacco) (Sanderson et al., 1997). Actual consideration of the relative carcinogenicity of the two agents depends on the level of consumption for each. Talamini and coworkers studied 60 nonsmoking drinkers and 32 nondrinking smokers and compared them to controls (Talamini et al., 1998). Depending on the amount of drinks per week, the OR reached 5.3 (95%CI = 1.1, 24.8) in the nonsmokers and 7.2 (95%CI = 1.1,-46) in smokers. Thus, the dose–response curves overlapped. In a pooled analysis of three studies form New York, Italy, and China, the OR for males with greater than 33 pack-years was 1.3 (95%CI = 0.6, 3.1) and for females who smoked more than 18 pack-years 4.6 (95%CI = 1.9, 10.9). Three published studies that report data by gender all indicate an increased risk for women compared to men, especially at the highest levels of smoking (Blot et al., 1988; Hayes et al., 1999; Muscat et al., 1996).

Cigarette type and oropharyngeal cancer risk have not been extensively studied. Three reports have not shown a difference between filter and nonfilter cigarettes (Blot et al., 1988; Hayes et al., 1999). Hand-rolled cigarettes appear to carry greater risks than manufactured cigarettes (De Stefani et al., 1998). Only one study could be identified that examined so-called tar content for cigarettes, and a lower risk was associated with low-tar cigarettes (La Vecchia et al., 1990). Black tobacco carried about a fivefold higher risk than blond (De Stefani et al., 1998). Where

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type among former smokers. Some data do not indicate a greater benefit for quitting in women compared to men (Halpern et al., 1993), although other studies do (Risch et al., 1993).

An overall challenge in assessing this cancer risk reduction is the question: Are quitters systematically different from current smokers and never smokers in ways that would explain the differences in cancer risks among these groups? A large, cross-sectional survey of nearly 9,000 adults in Britain (Thornton et al., 1994) attempted to answer this question by randomly sampling nonsmokers, ex-smokers, and current smokers in the population. The study collected data on a wide range of risk factors for poor overall health, including dietary, life-style, medical, and socioeconomic factors. Of 33 risk factors assessed, 27 were most prevalent among current smokers, and most risk factors decreased in prevalence with the amount of time since quitting. The data allowed estimation of the degree of confounding in smoking studies due to multiple risk factors and, importantly, called attention to the likely impact of these factors on epidemiological studies where weak associations are detected. In other words, the potential effects of confounding variables may be profound for weak associations between cancer and smoking variables, including those that attempt to estimate risk reductions among former smokers (where RRs have approached 1.5 or less and have been much debated). Finally, greater smoking and lower tendency to quit have been observed among socioeconomically disadvantaged groups relative to others, suggesting an increasing burden of tobacco-related cancers on persons of lower socioeconomic status. It should be noted that the MRFIT prospective trial found a higher lung cancer rate in the group with smoking cessation counseling versus usual care (Shaten, 1997). While this is likely due to chance alone, it may suggest that the greatest decrease in risk occurs in persons who are able to quit without counseling or that those who continue to smoke after counseling have high levels of exposure.

Many studies indicate that lung cancer mortality is increased for the first 5 years after quitting (Graham and Levin, 1971; Alderson et al., 1985; Halpern et al., 1993; Pohlabeln et al., 1997; Enstrom, 1999; Higgins and Wynder, 1988), which has been called the "quitting-ill" effect. It is presumed that this occurs because people who are ill are induced to quit. Although that is probably the explanation for this phenomena, it is not known if there is also some chronic induction of cytotoxicity or other mechanism in the lungs induced by tobacco smoking. When smoking ceases, this effect diminishes and allows already present neoplastic cells to replicate, so persons who would have developed lung cancer do so at a more rapid rate. This is currently speculative. The issue of biological evidence for tobacco harm among former smokers has been addressed in studies examining lung tissue biopsies. (Mao et al., 1997) compared LOH at several chromosomal loci in nontumor lung tissue samples from smokers, ex-smokers, and nonsmokers. LOH at 3p14 was found in 88% of smokers, compared to 45% in ex-smokers ($p = .01$) and 20% in nonsmokers. A similar pattern of increasing levels of genetic damage in current, former, and nonsmokers has also been reported with regard to p53 mutations in bladder tumors (Djordjevic et al., 2000). Witsuba et al., on the other hand, did not detect such differences in LOH at the loci they surveyed, but ex-smokers were just as likely as current smokers to have genetic changes typical of lung tumors, and these changes persisted many years after quitting (Wistuba et al., 1997). Thus, there do appear to be irreversible sequellae of past tobacco use even among people who have abstained for many years and are not currently diagnosed as having lung cancer.

In summary, stopping smoking decreases the risk of lung cancer, and the earlier that an individual stops, the greater is the reduction in risk. Data are not sufficient to determine whether certain levels of prior smoking result in proportionately greater or lesser risk reduction, although clearly, a greater smoking history carries a greater lung cancer risk (Graham and Levin, 1971).

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(PARs) of lung cancer among nonsmokers and ex-smokers. By far, the most important factor for female ex-smokers was their history of active smoking, explaining 56% of lung cancer incidence in the population of female ex-smokers and far outweighing factors such as environmental tobacco smoke (PAR = 1.7), occupational risk factors (PAR = 4), and family history of lung cancer (PAR = 14).

Unlike case-control studies, prospective studies can directly compute the relative risk of lung cancer among former smokers, and several large cohort studies have examined this in detail. (Doll and Peto, 1976) followed 34,440 British male physicians for 20 years and observed an age-adjusted annual death rate from lung cancer of 43 per 100,000 among ex-smokers, compared to 10 in nonsmokers and 140 in men smoking cigarettes exclusively. Thus, the rate was clearly lower than that in smokers but remained higher than that of nonsmokers. Results from the American Cancer Society's CPS-II of nearly 900,000 men and women, reported by (Halpern et al., 1993), demonstrated dose–response curves for the association of lung cancer mortality with years since quitting. For both men and women, the RR of lung cancer death by age 75 was <0.05 among lifelong nonsmokers compared to current smokers, while among ex-smokers who had quit in their thirties and forties, the RRs were in the range of 0.07–0.15. Even those who had quit at ages 60–64 experienced a reduction in risk of lung cancer mortality at age 75 (RR = 0.45 for men, 0.49 for women). The 20-year follow-up report on mortality among 12,866 participants in the Multiple Risk Factor Intervention (MRFIT) study observed a 60% reduction in deaths from lung cancer among ex-smokers compared to men who continued to smoke (Kuller et al., 1991).

Figure 12-5 shows the reduction in the RR of death from lung cancer among former smokers compared to those who continued to smoke from the large prospective cohort study of (Halpern et al., 1993). The amount of harm reduction depends not only on the length of time since quitting but also on the person's current age. Nonetheless, while the curves for each cohort of former smokers show downward trends for fatal lung cancer, the risk ratios never reach the low level experienced by persons who have never smoked cigarettes. Quitting at an earlier age provided the greatest risk reduction. In a logistic regression model, significant independent variables included gender, education, age (β = 0.085), number of cigarettes per day (β = 0.025), years smoked (β = 0.055), and years quitting (β depends on quit cohort). (Enstrom and Heath, 1999) compared lung cancer mortality among smokers and quitters in a cohort of 118,000 men and women in California born between 1900 and 1929 and traced from 1960 through 1997. Lung cancer mortality declined among ex-smokers, but never reached the rate experienced by people who had never smoked and was still twice as high after 20 years of quitting. This result is in agreement with the lung cancer mortality RR of 1.73 for people who had stopped smoking at least 15 years ago observed by (Enstrom, 1999) in the analysis of both National Health and Nutrition Examination Survey (NHANES I) data (N = 4,900) and a large veterans study (N = 284,000). Figure 12-6 shows (Enstrom's, 1999) results on the RR of fatal lung cancer according to the number of years since quitting, relative to men who never smoked. Note that the RR does not decline all the way to unity but remains modestly elevated (RR = 1.8) even after 15 or more years since smoking cessation. Such results (Enstrom, 1999) suggest the possibility that many former smokers are in poor health around the time of quitting, with substantial mortality with the first few years. This effect diminishes with time, and after 5 years the benefits become increasingly substantial among survivors. Other data show that risks of lung cancer shortly after quitting do not change much, but decrease to a 30% increased risk over nonsmokers after 10 years of cessation (Graham and Levin, 1971). No data are available to suggest differences in risk by cigarette

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from Norway, smokers who lacked GSTM1 also had an increased risk of lung cancer from p53 mutations, especially transversions (Ryberg et al., 1994).

Thus, it is important to study the differences in responses to PREPs by individual susceptibilities, in addition to gender, race, and diet, because they might increase or decrease product effectiveness in specific persons. In addition to carcinogen metabolism and DNA repair, genetic traits for other aspects of carcinogenesis and smoking behavior will undoubtedly be identified.

Former Smokers and lung cancer

Central to the issue of decreasing the harm from tobacco use in the general population is the evidence for lung cancer risk reduction among former smokers. The risk that is observed in former smokers can reasonably be predicted to be the lowest risk achievable by a PREP. This section describes studies of persons who quit smoking cigarettes and were not reported to have switched to other tobacco products.

The risk of lung cancer in former smokers is less than in current smokers, as demonstrated by both case-control and prospective studies. Case-control studies among former smokers are numerous and most have reported statistically significant reductions in the odds ratio of lung cancer relative to smokers. Some individual studies have been limited by the use of hospital controls, lack of adequate age adjustment, reliance on proxy interviews for information about the smoking behavior of deceased cases, and lack of information on potential risk reduction variability by histological type of lung cancer. A study conducted in Germany (Pohlabeln et al., 1997) addressed many of these issues. That study compared 839 lung cancer cases with an equal number of population-based controls matched on age, gender, and region and examined ORs by years since quitting and by histological type of lung cancer. Relative to current smokers, the lung cancer ORs among former smokers were 0.97 for those who had quit 10 years ago, 0.55 for 11–20 years since quitting, and 0.25 for those who had quit more than 20 years ago. The same pattern of OR reduction was observed among all histological types. In a separate study by Muscat and Wynder (Muscat and Wynder, 1995), the frequency of AD compared with SCC after 25 years of cessation appeared more like that in those who have never smoked than in current smokers. This was true for both men and women and is in agreement with other studies (Tong et al., 1996). Other studies indicate that risk differs depending on previous smoking history and duration of abstinence (Graham, 1971; Ben-Shlomo, 1994).

One of the difficulties in obtaining reliable estimates of the reduction in lung cancer risk among former smokers in case-control studies is the variability in the ages at which people take up smoking. In the study conducted by Sobue et al. in Japan (Sobue et al., 1993), all of the male former smokers had started smoking cigarettes between the ages of 18 and 22, a far narrower range than reported in many other case-control studies. In that study, the OR reduction for lung cancer among former smokers ranged from 50 to 65%, depending on the age at smoking cessation and the age at admission, with stronger benefits accruing to men who quit at younger ages and who were diagnosed at younger ages. This study also is noteworthy because it documented a hazard reduction even among men in their seventies who had stopped smoking for just a few years: the decrease in cancer risk among male ex-smokers of this age group is significant due to the higher incidence of lung cancer among men this age than in the general population. While the greatest absolute reduction in risk occurred among older smokers, the greatest rate of reduction in risk occurred among younger smokers.

(Alavanja et al., 1995) used case-control study data from 618 female lung cancer patients and 1,402 population-based age-matched controls to estimate the population attributable risks

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Factors Modifying Lung Cancer Risk

Although this report focuses– on the evaluation of PREPs, it also is recognized that other factors affect lung cancer risk, both positively and negatively (Lutz, 1999; Lee, 1997). These factors are not detailed here, but evidence follows to show that the evaluation of PREPs should consider other exposures and host susceptibilities that might affect an individual's risk related to PREPs. Many cancer risk factors covary with smoking consumption and thus can confound some studies (Thornton et al., 1994). Factors shown to modify cancer risk may include diet (Grinberg-Funes et al., 1994; Breslow et al., 2000; Mendilaharsu et al., 1998; Voorrips et al., 2000; Yong et al., 1997), vitamin use, and chemopreventive agents (Clapp et al., 1999; Omenn et al., 1996), although whether these factors actually modify cancer risk has not been conclusively demonstrated (Koo, 1997). While the latter might have sufficient impact because of dose, diet and vitamin supplementation would unlikely provide a significant benefit to proven harm reduction methods. This report does not consider these areas as potential harm reduction strategies.

Coexposures to other lung carcinogens from nonsmoking sources can lead to a multiplicative risk effect. These exposures include occupational asbestos exposure, occupational radiation exposure, radon, and therapeutic radiation exposure (Brownson, 1993; Jockel et al., 1992; Qiao et al., 1989; Inskip and Boice, 1994; Osann, 2000; Carstensen et al., 1988; Torkarskaya et al., 1995; Neugut et al., 1994; Tokarskaya et al., 1997; Moolgavkar et al., 1993). This report does not consider these coexposures in detail, but it should be recognized that they might affect the efficacy of PREPs. Prior lung disease history might increase lung cancer risk in smokers and persons exposed to TS (Mayne et al., 1999).

Heritable susceptibilities can affect tobacco-related cancer risks (Shields and Harris, 2000; Shields, 2000; Brockmoller et al., 1998). The use of genetic susceptibilities in the context of a given type of exposure can increase risk assessment prediction (Khoury and Wagener, 1995). Evidence for familial transmission of risks comes from analyses of lung cancer patients and their parents (Sellers, 1992; Sellers et al., 1992; Amos et al., 1999), although some studies have disagreed (Braun, 1994; Mayne et al., 1994). While these types of studies tend to implicate high-penetrance genes, there also is evidence that low-penetrance genes in carcinogen metabolism can modify cancer risks, and it is likely that other types of genes will also (e.g., DNA repair, cell-cycle control, apoptosis, signal transduction). Examples of frequently studied genetic polymorphisms in tobacco-related cancers that have been shown in some studies to modify smoking-related disease risk include the glutathione *S*-transferase M1 (*GSTM1*) (Kilmora, 1995; Lehman et al., 1996; Brockmoller et al., 1998, 1996; Rebbeck, 1997; Jourenkova-Mironova et al., 1999, 1998; Bell et al., 1993), cytochrome P-450 1A1 (*CYP1A1*) genes (Kihora, 1995; Ishibe et al., 1997), glutathione S-transferase Pi (Ryberg et al., 1997), and others (Sjalander, 1996; Bouchardy, 1998; Jourenkova-Mironova et al., 1999; Wiencke et al., 1997; Rosvold et al., 1995). These genetic polymorphisms and others are believed to affect levels of biomarkers, such as DNA adducts (Kato et al., 1995; Ryberg et al., 1997; Pastorelli et al., 1998;Yu et al., 1995). Interestingly, in Japanese, the risk for the GSTM1 null genotypes increases with increasing levels of smoking (Kihara and Noda, 1994), but the opposite is true for CYP1A1 (Nakachi et al., 1991), indicating a saturation effect. Also, several biomarker phenotypes representing carcinogen metabolism and DNA repair have been shown to modify the effects of smoking-related risks (Li et al., 1996; Spitz et al., 1995; Wei et al., 1996). More specific evidence for a relationship between gene–environment interactions and mutations in the p53 gene can be found from Japanese studies of CYP1A1 (Kawajiri et al., 1996), where a fivefold increase in risk was found for smokers with lung cancer. This risk increased further for persons who also lacked GSTM1. In one study

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the same level of tobacco consumption calculated as cumulative tar intake (Harris et al., 1993). African Americans tend to smoke menthol cigarettes, while the opposite is true for Caucasians (Cummings et al., 1987). Menthol cigarettes provide cooler smoke that helps anesthetize airways (Sant'Ambrogio et al., 1991), so smoking topography might be affected (Orani et al., 1991). The greater use of mentholated cigarettes among African Americans (Cummings et al., 1987; Wagenknecht et al., 1990) is associated with a higher lung cancer risk (Sidney et al., 1995), although not in other studies of menthol cigarettes (Kabat et al., 1991). In two studies the carbon monoxide (CO) boost was shown to be higher among users of menthol cigarettes (Clark et al., 1996; Jarvik et al., 1994), but not in another study that examined women (Ahijevych et al., 1996). Another mechanism for potential harm from mentholation is pyrolysis of menthol, which leads to benzo[a]pyrene production (Schmeltz and Schlotzhauer, 1968). Socioeconomic status may also contribute to racial differences in lung cancer incidence (McWharton, 1989).

African Americans tend to smoke less than Caucasians (Kabat et al., 1991; Vander Martin et al., 1990; Hahn et al., 1990; Royce et al., 1993), but may be more highly nicotine dependent (Vander Martin et al., 1990; Royce et al., 1993). They also tend to smoke higher-tar and nicotine cigarettes, resulting in higher nicotine levels and greater tar yields (Hahn et al., 1990; Perez-Stable et al., 1998). This is consistent with repeated findings of higher cotinine levels in African Americans compared to Caucasians (Wagenknecht et al., 1990; Caraballo et al., 1998) and higher urinary TSNAs in African Americans (Richie et al., 1997). Even though it was recently shown that African Americans have decreased cotinine clearance, rather than different nicotine metabolism (Perez-Stable et al., 1998), there is still the possibility of higher relative carcinogen exposure. For example, this study did not consider smoking topography. There are data showing that African Americans smoke more of their cigarettes (Clark et al., 1996) and have a higher CO boost per millimeter of cigarette smoked (Ahijevych et al., 1996; Clark et al., 1996). They also have higher nicotine intake per cigarette (Perez-Stable et al., 1998).

When considering a PREP, we must consider different races within the United States and other countries, where more environmental exposures are shared. In general, within levels of smoking, the risks of lung cancer around the world are similar, with some exceptions. In China, a combined analysis of studies that appeared in the Chinese literature reportedly demonstrated a dose–response relationship for men and women (Liu, 1992). However, the slope of the dose–response relationship was less than that in Western studies and similar to that for Japan. Importantly, the attributable risk for smoking was only 57% in men and 26% in women, where 88% and 46% of male and females smoked, respectively. A substantial number of Chinese also smoked pipes of various types, and among these individuals, the risk of lung cancer was lower than among persons who smoked only cigarettes (Lubin et al., 1992). Whether this represents a method of harm reduction remains unknown since that was not specifically studied, and the lower risk might have been observed for many reasons. Caution must be used in attempting to implicate any particular factor for differences in lung cancer rates in different geographical areas. These differences might be due to uses of different tobacco products, smoking topography, modifying effects of tobacco (e.g., diet), or increased frequencies of genetic traits. Separately, differences in health system access, reporting methods, or diagnostic procedures also may substantially affect the accuracy of risk estimates.

In summary, there are sufficient data to show that the use of tobacco products, exposures, and outcomes can vary in different racial and ethnic groups. Thus, PREPs must be assessed in the context of the ethnicity and race of intended users.

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cause they have begun smoking in recent times with lower-tar and nicotine cigarettes (Thun et al., 1997), which can deliver greater amounts of TSNAs (Hoffman and Hoffman, 1997). There is a lack of evidence, however, showing consistent differences in greater smoking topography, but this may be because both men and women were smoking similar types of cigarettes.

Another explanation for a higher lung cancer risk in women might be related to biological differences between men and women. There might be a hormonal relationship, because women more commonly have estrogen or progesterone receptors in lung cancer (Kaiser et al., 1996) (two studies found such a high abundance in both males and females, but a difference between the two could not be discerned [Su, 1996] (Canver et al., 1994) or by estrogens that can induce metabolizing enzymes. Also, because women suffer more tobacco withdrawal symptoms during menses, they might have greater lifetime exposure (Oltura, 1989). Women have higher levels of carcinogen–DNA adducts in lung tissues, even though they have the same or lower levels of smoking (Ryberg et al., 1994), which supports the latter hypothesis. Separately, Chinese women have a higher risk of lung cancer if they have more and shorter menstrual cycles (Liao, 1996; Gao et al., 1987). The frequency of p53 mutations is higher in men, consistent with the greater amounts of smoking, but women more commonly have G→T transversions (Kure et al., 1996), suggesting a particular susceptibility to tobacco smoke carcinogens. Women might also be more susceptible if they have particular metabolic polymorphisms that affect carcinogen detoxification (Rybert et al., 1997; Mollerup et al., 1999; Tang et al., 1998). Separately, gastrin-releasing peptide has been shown to be more highly expressed in women than men for the same level of smoking (Shriver et al., 2000). The gene for this peptide is located on the X chromosome, so a double copy might result in increased levels that in turn trigger growth stimulation. Therefore, assessment of PREPs also should consider possible effects on hormonal status and differences in the effects of individual tobacco constituents in women.

Racial and Ethnic Differences in Lung Cancer Risk

Lung cancer rates differ by race and ethnicity (USDHHS, 1998). Lung cancer incidence rates are highest among African-American males (112.3 per 100,000), followed by Caucasian males (73.1 per 100,000). African-American and Caucasian females have similar rates (46.2 and 43.3 per 100,000, respectively). Asian-American males and females have relatively lower rates (52.4 and 22.5, respectively), while Hispanics have the lowest rates (38.8 and 19.6, respectively). In the United States, smoking rates differ; African Americans, Hispanics, Chinese Americans, and Hawaiians tend to smoke fewer cigarettes per day than European Americans (Le Marchand et al., 1992). In the United States, Hispanic males and females tend to smoke less than non-Hispanic whites, but the risks within smoking levels are similar (Humble et al., 1985). Hawaiians have a greater risk of smoking compared to Filipinos and Caucasians living in Hawaii (Le Marchand et al., 1992). The differences in lung cancer rates within smoking categories may be due to smoking topography, types of cigarettes smoked, differences in the frequencies of heritable traits, and/or environmental, life-style, and dietary differences. For example, Japanese have lower rates of lung cancer than persons from other countries, which may be due to the use of tobacco with lower TSNAs, more frequent use of charcoal filters, or life-style differences. However, the effects of these factors on lung cancer rates are small compared to the overall increased risk for use of cigarettes.

There are some data to suggest that lung cancer risk is higher in African Americans than Caucasians for a given level of smoking (Harris et al., 1993; Schwartz and Swanson, 1997). For example, Harris et. al. reported an RR of 1.8 for African Americans compared to Caucasians at

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Most of the above studies suggest that the use of filtered or low-tar cigarettes was associated with lower lung cancer risk, even though there is clearly an increased risk of all types of lung cancer with all types of cigarettes. Ecological studies also support such a conclusion when smoking rates and lung cancer mortality over time are compared and the slopes for the decline in smoking are less steep than the decline in mortality (Trends, 1998; Peto et al., 2000). However, many significant considerations that make such data difficult to interpret. These studies assess smoking at a specific point in time, which prevents the collection of useful data later in prospective studies and is subject to recall bias in case-control studies. Indeed, assessing smoking prospectively at multiple time points or considering individual smoking improves estimates (Lee, 1998; Akiba, 1994). Separately, these studies do not account for cohort effects where the public's overall lung cancer risk may have changed due to diet and life-style or for the possibility that persons who smoke low-tar cigarettes otherwise differ from those who smoke high-tar cigarettes. Additionally, it is important to note that these studies do not provide an assessment of what happens to persons who switch cigarette type, which is directly relevant to assessing PREPs.

GENDER DIFFERENCES IN LUNG CANCER RISK

The prevalence of smoking among women is less than among men and consequently have overall lower rates of lung cancer (Shopland et al., 1991) and preneoplastic lesions (Lam et. al., 1999). However, lung cancer rates recently have been decreasing for men but not for women (Wingo et al., 1999). The rates of increase since the 1950s for lung cancer in general, and AD in particular, are higher for women than men, because of women have increased the amounts of cigarettes smoked per day, start smoking earlier, and smoke different types of cigarettes (Thun et al., 1997; Shopland et al., 1991; Levi et al., 1987; Haldorsen and Grimsrud, 1999). Women more commonly have AD than SCC, even after controlling for smoking status (Ernster, 1996). Several studies have provided evidence that women have a higher risk of lung cancer for a given level of smoking. In a study of 1,108 males and 781 females with lung cancer, compared to 1,122 male and 948 female controls, women were found to have a 1.2-to 1.7-fold higher risk, which was limited to AD and SCLC cancers, rather than SCC (Zang and Wynder, 1996). These data provided similar results when examined by estimated tar yields according to the FTC method, pack-years, and recent smoking per day. Other studies have provided similar findings Engeland, 1996; Lubin and Blot, 1984; Risch et al., 1993; Osann et al., 1993; Brownson et al., 1992; Cohn et al., 1996), although some have not (Doll and Peto, 1976; Halpern et al., 1993). While some might hypothesize that the difference in cancer risks between men and women are due to differing baseline nonsmoking rates (Prescott et al., 1998), this was found not to be the case using summary statistics from several large cohort studies (Risch et al., 1994). An increased risk in women is also evidenced by data showing that there is a higher risk for lung cancer in women at similar ages of initiation and the risks are the same for women who start smoking over age 25 as for men over age 20 (Hegmann et al., 1993). In a study of lung cancer risk among persons who switched from filtered to nonfiltered cigarettes, both women and men had a lower lung cancer risk if they smoked similar amounts of cigarettes per day before and after switching (Augustine et al., 1989). However, women had a greater likelihood of compensation and smoking more cigarettes, especially at lower doses. For similar levels of increased cigarettes per day, women had a much higher risk of lung cancer. There are several plausible explanations for this increased risk that bear directly on the effects of PREPs. The increased risk observed in women might be due to smoking behavior and/or biological differences. For example, women may be at higher risk be-

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lower-tar cigarettes, many do not, especially when risk is considered along with biomarkers in relation to smoking behavior.

Studies Assessing FilterCigarette Use. One of the earliest reports suggesting that filtered cigarettes were less hazardous than nonfiltered cigarettes was published by Bross and Gibson, who estimated a 60% decrease in risk in 265 cases compared to 214 controls (Bross and Gibson, 1968). Lubin and coworkers (Lubin et al., 1984) reported that nonfilter cigarette use compared to filtered cigarettes consistently gave higher RR estimates for lung cancer, no matter the history of cigarette smoking duration or cigarettes per day. Interestingly, the magnitude of the risk for cigarettes per day and years of use increased substantially more for persons using filtered compared to nonfiltered cigarettes. This suggests that decreasing cigarette use in persons using PREPs might have more easily demonstrable benefits. In other studies of filtered versus nonfiltered cigarettes, a decreased lung cancer risk of 30% was found in a French study of 1,625 lung cancer cases and 3,091 controls (Benhamou, 1985, 1989), a twofold lower risk in a Philadelphia study (Khuder et al., 1998), a 3.5 fold decrease in an Argentinian study (Pezzotto, 1993) and a fourfold decrease for women in a Spanish study (Agudo et al., 1994). Wynder and Stellman (Wynder and Stellman, 1979) reported that among 684 cases and 9,547 controls, there was a reduced risk for those who smoked of nonfiltered cigarettes for 10 years or more, although the results were not statistically significant. However, when they later reported data for 1,242 lung cancer cases compared to 2,300 controls and accounted for increasing smoking per day after switching to lower-tar cigarettes, they found that lung cancer risk was not reduced and even increased in the highest levels of compensation (Figure 12-4) (Augustine et al., 1989). Other studies also have reported a reduced risk for filtered cigarettes (Rimington, 1981; Pathak et al., 1986), but a dose–response relationship for persons who mix their brands was harder to demonstrate (Lubin et al., 1984; Pathak et al., 1986). Lee and Garfinkel provided a summary of lung cancer risk and type of cigarette smoked (Lee and Garfinkel, 1981) and concluded that there was about a 25% reduction in lung cancer mortality for filtered cigarettes. In this review as in others, there was no consideration of biomarkers, actual smoking consumption, or analysis for persons who switched cigarette types. Several studies do not support a decreased risk for filtered cigarettes. In a population-based case-control study, when amount of smoking was considered, there was no benefit from filtered cigarettes (Wilcox et al., 1988). Data pooled from four cohorts failed to show a statistically significant benefit for filtered cigarettes and lung cancer risk, even among different levels of smoking (Tang et al., 1995), as did another large cohort of 79,946 members of Kaiser Permanente (RR = 1.03 for men and 0.65 for women; neither was statistically significant), although women who used filtered cigarettes for more than 20 years had a risk of 0.36 (95%CI = 0.18, 0.75) (Sidney et al., 1993).

In comparison to nonfiltered cigarettes, filtered cigarettes are more closely associated with AD rather than SCC (Pezzotto, 1993; Stellman et al., 1997), although this was observed mostly in women smokers in another study (Stellamn, 1997; Lubin and Blot, 1984). Hand rolled cigarettes had an increased risk for SCC and not AD (Engeland et al., 1996). This association is thought to be due to greater depths of inhalation when the filter is in place to compensate for lower nicotine amounts, as well as increased delivery of TSNAs. Evidence for this includes self-report of frequency and depth of inhalation associated with AD rather than SCC (Lubin and Blot, 1984). When considering persons who switched from nonfiltered to filtered cigarettes, compared to lifetime nonfilter cigarette smokers, there was a decrease in risk for SCC but not AD in men and women (Stellman et al., 1997).

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(CPS-1) Cohort study had a lower standardized mortality ratio (SMR) for persons who smoked lower-tar cigarettes within smoking amount categories (Stellman and Garfinkel, 1989). The SMRs increased from 841 to 1,236 in smokers using cigarettes with less than 17.6 mg for the lowest-tar category and more than 25.7 mg for the highest-tar category. The greatest proportional increase was in persons who smoked the highest number of cigarettes per day. An important limitation of this study was that no adjustment was made for smoking duration, with the claim that an age adjustment approximated this need, although models of lung cancer risk do not support this assumption (Moolgavkar et al., 1989). It also classified tar exposure based on current cigarette use, rather than usual brand smoked or switching. A hospital-based case-control study of 881 cases and 2,570 controls indicated that there was a threefold increased risk from smoking 22–28-mg tar cigarettes compared to less than 22-mg tar cigarettes, which increased to fourfold for more than 29 mg. (Kaufman et al., 1989) Lubin and coworkers (Lubin et al., 1984) studied 7,804 lung cancer cases and 15,207 hospital-based controls in five different European cities. This study collected data for previously used cigarette brands, up to a maximum of four, and considered cigarettes per day and duration for each of those brands. So-called total tar exposure was estimated, and a statistically significant trend for increasing risk with highest-tar exposure was observed in both men and women. Compared to persons who only used low-tar brands, person who used other brands less than 25% of the time had a risk of 1.2, using other brands more than 25% of the time led to a risk of 1.5; using high-tar brands more than 75% of the time led to a risk of 1.8; and exclusive use of high-tar brands produced risk of 1.7. By contrast in another study (Benhamou et al., 1985), the risk of mixing cigarette types was no different than exclusive use of nonfiltered or dark-tobacco cigarettes (Benhamou et al., 1994), where data were provided for smoking duration and cigarettes smoked per day, and there was no clear subgroup (high or low levels of smoking) that had a particularly higher or lower risk compared to low-tar or filtered cigarettes. In a hospital-based case-control study by Alderson and coworkers, reported switching to filtered cigarettes for either less than or more than 10 years before lung cancer diagnosis did not show a statistically significant difference in difference risk (Alderson et al., 1985). The potential for increasing consumption when switching brands is important and can modify the possible benefits of presumed lower-tar exposure, as shown in a case-control study of 763 cases and 900 controls by Wilcox and coworkers, in which increasing weighted average tar yields crudely predicted increased risk until exposures were controlled for by cigarettes per day, duration, or pack-years (Wilcox et al., 1988). The Wilcox group, interestingly, concluded that there was more compensation by increasing cigarettes per day in cases compared to controls that switched to lower-tar and nicotine cigarettes. Data pooled from four cohorts failed to show a statistically significant benefit for low-tar cigarettes in terms of lung cancer risk, even among different levels of smoking (Tang et al., 1995), as did another large cohort study (Sidney et al., 1993). Lee and Garfinkel provided a summary of lung cancer risk and type of cigarette smoked (Lee and Garfinkel, 1981) and were unable to demonstrate a significant decrease in risk based on tar content. There was some observed benefit in terms of tar content when comparing high-to low-tar cigarettes but not for medium versus high tar. Thiocyanate levels, which reflect quantity of cigarettes per day and smoking topography, are associated with increased lung cancer risk, whereas the tar yields of cigarettes were not (Kuller et al., 1991).

Case-control studies have provided evidence that black tobacco carries almost a fourfold risk higher risk tan blond tobacco (Benhamou, 1985, 1989; Joly, 1983), and a 6.6-fold higher risk in women (Agudo et al., 1994).

In summary, while some studies suggest that there is a lower risk of lung cancer with

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A PREP would have to work by reducing exposure, but there are few data today to provide an estimate of how much reduction would have a measurable effect in disease outcome. Studies that examine switching to lower amounts of smoking are few. Benhamou and coworkers reported that compared to 1,503 controls, 1,057 lung cancer patients who reported decreasing daily cigarette use by more than 25% had a 20% reduction in risk, although this was not statistically significant (Benhamou et al., 1989). Lubin, et al. reported that reducing daily consumption by more than 50% reduced risk by about 16%, which was barely statistically significant (Lubin et al., 1984). Thus, the data available is not sufficient to suggest how much decreased consumption must occur to show a measurable benefit. Wald and Watt (Wald and Watt, 1997) reported that persons who switched from cigarettes to pipes or cigars had a higher risk of lung cancer than persons who had never smoked cigarettes. They also found that these individuals inhaled more of their cigars and pipes; so while there was a reduction in risk compared to continuous cigarette smoking, their was still a persistent effect (Wald and Watt, 1997). Graham and Levin found a sixfold increased risk in persons who switched from cigarettes to other tobacco products, compared to an 8.8-fold risk of continued cigarette use and a 2.6-fold risk for persons who had only smoked other tobacco products and continued to smoke them (Graham and Levin, 1971). This represented a 27% reduction in risk compared to continued smoking.

Lung cancer risk and cigarette type

An important question is whether smoking low tar and nicotine cigarettes is associated with lower lung cancer risk and whether switching to such cigarettes has shown a benefit. The available data can be summarized as those that examine risk in relation to tar content or to the use of filtered cigarettes. It is important to understand that there are few differences in type of tobacco used among commercial cigarettes and that most changes in tar and nicotine delivery are achieved mainly through the use of a filter, which affects the absorption of carcinogens as well as diluting the smoke with air through ventilation holes. Thus, under similar smoking circumstances (which does not happen in humans), the amount of tar that would be delivered from a cigarette varies in the following order from the highest to the lowest: nonfilter, filter high tar and filter low tar. Confounding this relationship, however, the fact is that over the past 30 years, the amount of tar yield per cigarette type has also decreased.

While the studies described below indicate a lesser risk in lung cancer for low-tar and nicotine cigarettes, there are outstanding questions about smoking behavior that might affect the interpretation of epidemiological studies. While it is possible to examine risks for persons who smoke low-tar and nicotine cigarettes, the perceived decreased risk may be due to several confounding variables that have not yet been measured. For example, such individuals might be smoking these cigarettes because of a desire to quit or reduce their smoking, and so might smoke less of their cigarettes, have more quitting attempts, or underreport what they smoke. They also might have some illness (i.e., respiratory problems) that may lead them to reduce the amount they smoke. Finally, these may be individuals who have "healthier" life styles (e.g., diets that reduce lung cancer risk).

Studies Assessing Tar Content. Several large studies have suggested that higher-tar cigarettes are associated with increased lung cancer risk or that the risk is less for smokers of low-tar cigarettes compared to high-tar or mixed exposures (Benhamsu, 1985; Lubin et al., 1984; Stellman and Garfinkel, 1989; Kaufman et al., 1989; Vutuc and Kunze, 1983). Other studies have not shown a reduced risk due to low-tar cigarettes (Kuller et al., 1991; Wilcox et al., 1988; Lee and Garfinkel, 1981; Sidney et al., 1993). The American Cancer Society Cancer Prevention Study

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In contrast, Law and coworkers (Law et al., 1997) argued that if smoking data in cohort studies were adjusted for actual internal exposure, in their case predicted by carboxyhemoglobin levels, then the shape of the curve assumes a quadratic relationship, where the slope is higher at more than 20 cigarettes per day; these authors argue that a quadratic relationship is more biologically plausible (Figure 12-3). This data imply that the greatest effect of harm reduction would occur in smokers with the highest levels of baseline smoking. Because of these conflicting models, it is impossible at this time to conclude a lesser or greater benefit from exposure reduction at higher or lower levels of smoking. However, the argument by Law and coworkers for including an internal exposure assessment are compelling (Law et al., 1997). Therefore it is likely that the use of biomarkers would provide better estimates of dose–response relationships and harm reduction. It also should be noted that the above analyses that derive models for dose–response relationships mostly do not consider duration of smoking. It is possible that the daily consumption of cigarettes and lung cancer risk have different relationships based on the number of years smoked (Mizune and Akiba, 1989; Rylander et al., 1996).

The available cohort studies do not provide data that allows for modeling at smoking levels of less than 10 cigarettes per day, which is important for understanding the effects of PREPs that result in low exposure levels. Models developed by (Puntoni et al., 1995) for smoking less than an average of 1.4 cigarettes per day do not indicate the existence of a threshold, and there are no current data today to show where one might exist. It should be noted that thresholds are difficult to demonstrate (Purhovic, 1995). Puntoni and colleagues (Puntoni et al., 1995) predict an increased risk for smoking at levels as low as 0.25 cigarette per day. Depending on the model however, there are different slopes for low-dose exposures, where a Weibull model predicts a rapid rise to a relative risk (RR) greater than 2 at 0.2 cigarette per day. A multistage model, however, shows a linear response at low levels of exposure. Either model, however, indicates that the best goal for harm reduction is complete cessation because there are risks at the lowest levels of smoking, and no safe level can be discerned from the literature. It has been estimated that ETS exposure is equivalent to approximately one cigarette per day (Vutuc, 1984), and although this seems to be a small amount, the risk will depend on duration of exposure as well. Thus, while ? is thought to exist (Teeguorden, 1988), it has not been shown for tobacco exposure.

Biomarker studies have attempted to establish a dose–response relationship for smoking, but the relationship has been variable. Most studies crudely examine smokers versus nonsmokers, rather than reporting a relationship by levels of smoking. Dallinga and coworkers (Dallinga et al., 1998) determined 4-ABP–hemoglobin adducts and "total" ^{32}P-postlabeled DNA adducts in peripheral lymphocytes in 55 smokers. The slope of the response was greater for the "total"phosphorus-32 postlabeled DNA adducts than for the 4-ABP-hemoglobin adducts in relation to cigarettes per day, and a third-order polynomial curve best fit the data. A plateau began at about 10 cigarettes per day for the former and 20 cigarettes for the latter. In this same study, so-called tar consumption per day had a similar effect. The correlation coefficients for tar were higher than for cigarettes per day, but no models were presented that would allow one to assess the relative contribution of tar versus cigarettes smoked per day, and topography was not considered. The data suggest that for a given level of cigarettes per day, the type of cigarette affects the adduct levels, but that at certain higher levels of cigarettes per day, there is less adduct formation per cigarette. This might be due to differences in smoking topography at higher levels of smoking or saturation of metabolic, repair, and apoptotic capacities. All of these factors probably play a role and have led to differences in adduct formation rates in hemoglobin and in lymphocytes.

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Dose–response for smoking and lung cancer

The evaluation of a PREP would include an assessment of how the dose–response curve for smoking is altered as exposure is reduced. Today, however there are limited data on the effects of decreasing exposure short of complete cessation. When people stop smoking, their risk of lung cancer decreases over time. Thus, it is plausible that exposure reduction short of cessation may also reduce risk. One might be able to predict the effects of a particular harm reduction method by assuming that the risk for a smoker who achieves exposure reduction will drop to that of a continuous lower-level smoker. This assumption would be speculative at present and it must be evaluated through an understanding of the dose–response relationship of smoking to lung cancer. The modeling for a PREP, however, might be more complicated and analogous to intermittent exposure situations (Murdoch, 1992).

A dose–response relationship between cigarette smoking and lung cancer has been established in cohort studies of both men and women (Shaten, 1997; Thun, 1995; Tuerdal, 1993; Friedman, 1979; Chyou, 1992; Engeland, 1996; Nordlund et al., 1997; Winter et al., 1985; Doll and Peto, 1976). These studies show remarkable consistency. Both daily smoking amounts and duration of smoking are important contributors to risk, although the lung cancer risk ratios for daily smoking are higher than for duration of smoking. An earlier age at initiation is a separate lung cancer risk factor (Benhanisu, 1985; Hagmann et al., 1993; Benhamou et al., 1994; Khuder et al., 1998). Zang and Wynder had proposed to estimate cumulative tar exposure by determining all brands used for different periods of life and the quantity per day for a person, using milligram yields calculated by the FTC method (Zang and Wynder, 1992). The reported effect of how deeply someone inhales also has been associated with an increased risk (Agudo, 1994; Wahai, 1997; Joly, 1983; Benhamou et al., 1994; Khuder et al., 1998). There is some data to indicate that smoking more cigarettes per day increases the risk for small cell carcinoma (Weiss et al., 1977).

The slope of a dose–response curve may provide an indication of the success of a PREP in smokers. Several groups of investigators have modeled different cohort study sets for lung cancer and have found different relationships. Using data from single studies, (Armitage, 1985) and (Gaffney and Altshuler, 1988) provided evidence that smoking risk fits either a multistage or a two-stage model for initiation and cell proliferation. (Doll and Peto, 1978) found that their data on British doctors fit a second-order polynomial equation for number of cigarettes per day and a quadrate equation for duration, although this was only true for smoking less than 40 cigarettes per day. Reanalysis of their data using different approaches confirmed the quadratic function where any two of three dose-dependent parameters (cigarettes per day, duration, age) were considered and the greatest predictor was cigarettes per day (Moolgavkar et al., 1989). A linear relationship was reported in Japanese men (Mizuno and Akiba, 1989), with duration identical to the estimate of (Doll and Peto, 1978). Puntoni and coworkers summarized data for nine different cohort studies and found that a multistage model best fit the data ($R^2 = 0.67$, which increased to 0.80 when one study was eliminated) (Figure 12-2) (Puntoni et al., 1995). Logit, Probit, and Weibull models also provided a good fit (all $R^2 = 0.61$), but a one-hit model provided a poor fit ($R^2 = 0.36$). As a validation step, the authors included data for passive smoking and the fit was acceptable. Importantly, these models all predict a greater slope for increasing risk at lower doses and a plateau at higher doses. The multistage model showed that risk increased to a plateau at about 20 cigarettes per day, while the Weibull model showed a decrease in the rate of increasing risk at about 5 cigarettes per day. The latter model, however, never clearly reaches a plateau so that any decrease in smoking might have some benefit. These data imply that small amounts of exposure reduction at higher levels of smoking may not be sufficient to achieve harm reduction.

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Sekido et al., 1998), but because they have not been directly linked to smoking, they are not discussed here.

Overall allelic losses (Wistuba et al., 2000) and mutations of the p53 gene (Chiba et al., 1990; D'Amico et al., 1992) are more common in SCLC and SCC than in AD. For p53, a positive relationship exists between lifetime cigarette consumption and the frequency of mutations (Ahrendt et al., 2000), and of G→T transversions in particular (Kondo et al., 1999), and these lesions are more common than G→A transitions. Supporting the role of PAHs in p53 mutations, benzo[a]pyrene-diol epoxide and other PAHs bind to guanine at codons 157, 248, and 273 of the p53 gene (Smith et al., 2000; Denissenko et al., 1996), which are hotspots for the G→T transversions (Denissenko et al., 1997). Never smokers who develop lung cancer have a completely different, almost random grouping of p53 mutations (Rom et al., 2000; Ahrendt et al., 2000). Alcohol consumption might further increase the frequency of p53 mutations (Ahrendt et al., 2000).

The contribution of DNA repair pathways to lung carcinogenesis has had limited study. Increased frequencies of microsatellite alterations (single shifts of nucleotides), rather than microsatellite instability (multiple shifts of multiple nucleotides), are seen in 20–30% of lung cancers (Fong et al., 1999), suggesting defective DNA repair through a mechanism similar to that seen for colon cancer and defective mismatch repair. Separately, mutations in the mitochondrial base excision repair enzyme, *OGG1* have been seen (Chevillard et al., 1998). Also reported is O^6-alkyl-alkylguanine transferase mutations (Wang et al., 1997), which might increase susceptibility to *N*-nitrosamines.

There are nonmutational effects of smoking in lung carcinogenesis. For example, telomerase expression is very frequent in lung cancer (Fong et al., 1999), which is increased in smokers compared to nonsmokers and former smokers, suggesting that this is reversible (Xinarianos et al., 1999). Expression of gastrin-releasing peptide is seen in lung cancer in response to tobacco smoking (Shriver et al., 2000), and might contribute to bronchial epithelial cell proliferation before lung cancer develops. Some data exist to implicate nicotine as the inducer of gastrin-releasing peptide (Shriver et al., 2000). Hypermethylation of promoter regions, such as that for p16, death-associated protein kinase, glutathione *S*-transferase P1, estrogen receptors and O^6-alkyl–alkylguanine transferase have frequently been observed in lung cancer,[30] and smoking in particular has been associated with an increased frequency of hypermethylation of p16 (Belinsky et al., 1998). Reactive oxygen species, produced by tobacco smoke constituents, as well as through inflammatory responses, can affect many different protein kinases and transcription factors (Minamoto et al., 1999). How these effects influence carcinogenesis is currently unknown, but perturbations in the balance between oxidative stress and response clearly affect cell survival.

Lung cancer survival after surgical resection and for more advanced stages might be affected by smoking history (Xavier, 1996; Hendriks et al., 1996; Hinds et al., 1982; Sekine et al., 1999), especially in the earlier years after surgical resection (Sobue et al., 1991). While women who smoke might be diagnosed at later stages because their symptoms have been ignored, the early-stage data supports relationship between smoking history and survival of lung cancer patients. Smoking also increases the risk of lung metastases in breast cancer patients (Scanlon et al., 1995) and of second primary cancers after the diagnosis of lung cancer (Levi et al., 1999). Thus, a PREP in a person with lung cancer or breast cancer might be beneficial, in addition to reducing risks for secondary cancers.

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due to the use of lower-nicotine cigarettes, increased exposures to TSNAs and greater depths of inhalation.

Lung cancer is preceded by a series of histopathological changes. These changes have been identified for SCC and consist of both reactive changes (hyperplasia, metaplasia) and preneoplastic changes (dysplasia, carcinoma in situ [CIS]) (Auerbach et al., 1961). These histologic changes occur far less frequently in never smokers than in cigarette smokers and increase in frequency with the amount of smoking, adjusted for age (Auerbach et al., 1979). Advanced histologic changes are rarely seen in nonsmokers, but occur in 2.6% of those who smoked 1 to 19 cigarettes a day, 13.2% of those who smoked 20 to 39 per day and 22.5% of those who smoked 40 cigarettes or more a day. Advanced bronchial preneoplastic changes (moderate to severe dysplasia and CIS) do not regress on smoking cessation, persist for many years, and possibly persist for life. Compared to men, women have a lower prevalence of high-grade preinvasive lesions in the observed airways (14% vs. 31%; odds ratio [OR] = 0.18; 95% confidence interval [C.I].= 0.04, 0.88) (Lam et al., 1999). Bronchial preneoplastic lesions are difficult to identify by routine white-light bronchoscopy but may be visualized by fluorescence bronchoscopy (Lam et al., 1998). Preneoplastic lesions preceding SCLC and AD are not well defined. AD has been associated with the presence of peripheral lesions known as atypical adenomatous hyperplasia (Kerr et al., 1994), while SCLC may arise directly from histologically normal or reactive epithelium (Wistuba et al., 2000).

Extensive molecular changes already are present in the bronchi of smokers before any morphological changes can be discerned (Mao, 1996; Wistuba et al., 1997). Allelic losses at chromosome regions 3p and 9p are present in about 80% of smokers, but are rarely present in those who have never smoked. Approximately one-third of the bronchial epithelium of smokers with lung cancer has sustained molecular damage (Park et al., 1999). These changes are more frequent and extensive in SCLC, intermediate in SCC, and much less frequent in AD (Wistuba et al., 2000).

Allelotyping of human lung cancers indicates multiple sites of frequent allelic (>30%) (Virmani et al., 1998) loss, which may represent the sites of recessive oncogenes. Loss of heterozygosity (LOH) on chromosomes 11 and 17 occurs more frequently with increased smoking (Mao et al., 1997; Schreiber et al., 1997). A molecular technique known as comparative genomic hybridization (CGH) permits identification of genomic sites of allelic loss as well as sites of amplification. CGH studies of human lung cancers and cell lines confirm allelotyping data and indicate that multiple sites of increased copy number are present in lung cancers, including c-MYC (Levin et al., 1995; Petersen et al., 1997).

Oncogene mutation frequency in lung cancers varies with the histological type. Ras gene mutations are present in about 30% of adenocarcinomas but are relatively rare in other lung cancers (Gealy, 1999; Slebos and Rodenhuis, 1992). It has been reported that ras mutations are present only in smoking-related cancers and that these mutations are associated with cigarette smoking (Reynolds, 1991; Slebos et al., 1991). Such mutations also can be observed in persons without lung cancer, suggesting that they may be an early marker of smoking-related damage (Slebos et al., 1991 Lehman et al., 1996; Yakubovskaya et al.,1995; Scott et al., 1997; Valkonen and Kuusi, 1998). Interestingly, the K-RAS mutations are G→T transversions, typical of PAH exposure (Gealy, 1999; Slebos et al., 1991; Hutchison et al., 1997). LOH affecting at least one locus of the FHIT gene was observed in 80% of lung cancers in smokers, but in only 22% of cancers in nonsmokers (Sozzi et al., 1998). These findings suggest that FHIT is a candidate molecular target of carcinogens contained in tobacco smoke. Many other molecular changes are present in lung cancers, such as the ERB-B family and MYC (Hecht, 1999; Fong et al., 1999; Kanetsky et al., 1998;

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disease risk is unknown. Several types of assays are available. The main limitation today is that no assays have convincingly been shown to be sufficiently predictive of cancer risk, so they can not be used singly to predict harm reduction. Chromosomal damage can be measured using classical cytogenetic methods (Obe, 1982), micronuclei formation (including in bronchial mucosa; Lippman et al., 1990) (Schmid, 1975; Xue et al., 1992), COMET (Speit and Hartmann, 1999; Poli et al., 1999), fluorescent in situ hybridization (FISH), or polymerase chain reaction (PCR) methods assessing loss of heterozygosity (using tandem repeats or comparative genomic hybridization), where the latter two methods can be used for morphologically appearing cells. Use of mutations in reporter genes, such as HPRT (Hou, 1999; Duthie, 1995; Jones, 1993; Ammemheura, 1997) (Hou et al., 1999; Bailar, 1999) or glycophorin A (GPA) have been used, but it is better to identify mutation rates in cancer susceptibility genes such as p53 (Ciruzzi et al., 1998; Yang et al., 1990; Brennan et al., 1995; Kure et al., 1996; or K-ras (Geally, 1999; Mills, 1995; Slebos et al., 1991; Yakubovskaya et al., 1995; Scott et al., 1997; Valkonen and Kuusi, 1998).

Biomarkers of potential harm that reflect later stages of carcinogenesis include morphological markers of preneoplastic lesions (e.g., dysplasia), altered phenotypic expression of normal cellular function (e.g., overexpression of the proto-oncogene Erb-B2), and mutations in cancer-related genes such as the p53 tumor suppressor gene. It is possible to measure p53 mutation rates in normal tissues (Hussain and Harris, 1999) of persons without cancer and to measure mutations in sputum for persons with cancer (Sidransky, 1997). Although these assays are available, current technology limits their use for large-scale epidemiological studies. It also has been found that measuring loss of heterozygosity (Mao et al., 1997) or hypermethylation of genes involved in neoplasia (Belinsky et al., 1998) might be useful for assessing the effects of tobacco smoke.

The study of p53 tumor suppressor genes in tumors might be helpful in determining which tumors were related to specific etiologies. It has been reported that there is a dose–response relationship between tobacco smoking and p53 mutations in general[199] and for G→T transversions in particular (Takeshmia, 1993) (Takagi et al., 1998; Kure et al., 1996). Women have more G→T (guanine-to-thymin) transversions than men for similar levels of smoking, even though men have p53 mutations more commonly (Kondo et al., 1996; Kure et al., 1996). In vitro studies show that BaP and other PAHs cause the same types of lesions, but in different parts of p53 (Smith et al., 2000). An interactive effect of alcohol drinking and cigarette use in oral cavity and lung cancers leads to different types of p53 mutations (Ahrendt, 2000) (Brennan et al., 1995). Interestingly, given that the p53 mutational spectrum for lung cancer is similar worldwide (Hartmann et al., 1997), tobacco smoke is likely the major determinant of lung p53 mutations worldwide.

LUNG CANCER

In this country, there were about 171,000 newly diagnosed lung cancer cases in 1999; 92.6% of these were incurable (Landis et al., 1999). Lung cancer consists of four major histological types, namely squamous cell cancer (SCC), small-cell lung cancer (SCLC), adenocarcinoma (AD), and large-cell carcinoma (LCC) (Travis et al., 1995). The first two types tend to arise from the large or medium-sized bronchi ("central tumors"), while the latter two tend to develop from the small bronchi, bronchioles, and alveoli ("peripheral tumors"). There has been a shift in the prevalence of histology types over time, in which AD has been increasing relative to SCC (Travis et al., 1995; Thun et al., 1997; Charloux et al., 1997). In Connecticut from 1959 through 1991, associations between cigarette smoking and death from AD versus SCC increased nearly seventeenfold in women and nearly tenfold in men, while smoking-related lung cancer risk increased from 4.6 to 19 in men and 1.5 to 8.1 in women (Thun et al., 1997). This is presumably

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biologically effective dose, and potential harm. Examples of how biomarkers might be applied to the assessment of PREPs are provided in Table 12-4. Epidemiological studies of lung cancer as the outcome would provide the best evidence for the use of a PREP. However, these studies have many pitfalls (Table 12-5), and more importantly, the assessment of a particular product would be difficult because of the short duration of use and changes in these products as technology develops, which would make it difficult to assess the risk of any individual product among all the others. (See Chapter 11 for a detailed discussion of biomarkers.)

The biologically effective dose (Perera, 1987) is the amount of a tobacco smoke or tobacco toxin that measurably binds to, or alters, a macromolecule (e.g., protein or DNA) in a cell. The biologically effective dose represents the net effect of metabolic activation, decreased rate of detoxification, decreased repair capacity, loss of cell cycle checkpoint control, and decreased rates of cell death. It should be noted that not all binding to, or alteration of, a macromolecule leads to an adverse health effect, and so often we are really measuring the dose to a target macromolecule that estimates a biologically effective dose.

For cancer, a common assessment of the biologically effective dose is the measurement of carcinogen-DNA adduct levels (Farmer, 1999). These are formed when carcinogen metabolites are alkylated to nucleotides, creating a promutagenic lesion. There are strong laboratory animal data and some human studies that prove a relationship between tobacco smoke constituents, carcinogen-DNA adduct formation, and cancer (La and Swenberg, 1996; Farmer, 1999). Laboratory animal studies have shown a cancer correlation with increased adducts in target organs (Nakayama et al., 1984; Ashurst et al., 1983; Pelkonen et al., 1980). In humans, tobacco smoking leads to increased adduct formation in target tissues such as the lung (Phillips, 1990 and 1996; Bartsch, 1991; Schoket et al., 1998; Wiencke et al., 1995; Phillips et al., 1988) and in surrogate tissues such as the blood (Wiencke et al., 1995; Vineis et al., 1994; Tang et al., 1995; Hou, 1999; Phillips, 1990 and 1996; Bartsch, 1991). Evidence exists that carcinogen-DNA adducts levels in target and non-target organs are modulated by interindividual differences (Kato et al., 1995; Ryberg et al., 1997; Rojas et al., 1998; Badawi et al., 1995; Stern et al., 1993; Grinberg-Funes et al., 1994; Pastorelli et al., 1998; Bartsch, 1991).

In humans, only a few studies have investigated a link between carcinogen-DNA adducts and cancer risk. All data come from case-control studies of the lung and bladder, and all show a positive relationship (Tang et al., 1995; Dunn et al., 1991; Van Schooten et al., 1990; Peluso et al., 1998). However, since no published prospective studies show a relationship of adducts to cancer, the case control studies must be interpreted cautiously because they may suffer from differential metabolism or DNA repair due to case status. A variety of assays are available to determine carcinogen-macromolecular adducts in human tissues (La and Swenberg, 1996; Farmer and Shuker, 1999; Hecht, 1999; Lee et al., 1993; Wang et al., 2000). These are reviewed in Chapter 11, along with data indicating which markers are useful for assessment in target organs.

Biomarkers of potential harm can range from isolated early changes with or without effects on function to events that clearly lead to carcinogenesis and can be observed in cancer cells. Assessing PREPs through clinical and epidemiological studies would consider this full range of effects. These studies are better focused on the earliest events that have been linked to disease, so that the adversity of disease is not a consequence. One goal has been to develop a molecular fingerprint of genetic damage that reflects a particular exposure in persons without cancer, although this has not happened for tobacco carcinogens, and any measurable effects are nonspecific. Nonetheless, a reduction in the level of genetic damage would logically be required if a PREP were to be successful, although the amount of reduction needed to derive a benefit in terms of

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cinogens are mutagenic. Chemicals that are not predictive of reactivity and are nonmutagenic are carcinogenic less than 5% of the time and so animal testing of nongenotoxic chemicals is less reliable without understanding the mechanistic etiology or carcinogenesis (Cohen, 1995). Concordance among animal species for the same organ site is less than 50%, almost that predicted by chance (Haseman and Lockhart, 1993; Gold et al., 1992). Importantly, the actual concordance might vary between 20 and 100%, where the currently observed concordance among rats and mice might be estimated wrongly due to measurement error (Haseman, 1992) (Freedman et al., 1996). Other studies indicate that concordance from rat to mouse occurred more commonly for chemicals that induce tumors at different sites, chemicals that induce tumors in both sexes, those that have a reduced latency, and those that increase the rates of rare tumors (Gray et al., 1995; Tennant and Spalding, 1996). Thus, if these same criteria are considered to apply in humans, it is less likely that there would be concordance for studies assessing changing levels of tobacco constituents as a way to assess PREPs. In general, the concordance between animal and human experience also is highly variable (Lutz, 1999; Monroe, 1994) (Gold et al., 1992), although carcinogens that are more potent in one species tend to be more potent in others, including humans. The major reason for differences in extrapolation from experimental systems to humans is that in vitro cell cultures and experimental animals from different species handle chemical exposures, DNA damage, and stress differently.

The inclusion of biomarkers in experimental animal studies with analogy to human exposures would be helpful.[7] Carcinogen–DNA adduct levels correlate with tumor incidence for the target organ of these animals (Farme, 1994) (Pledger et al., 1977; Ross et al., 1990). In some cases, target organ specificity is only approximate; for example, in benzo[a]pyrene-treated animals, levels are almost equal in liver and lung, but there is a higher cancer incidence in the former (Ross et al., 1990). Adducts of different classes have relatively similar potency (i.e., the number of adducts correlated with tumor induction is within one to two orders of magnitude) (Otteneder and Lutz, 1999). One limitation is that adduct levels associated with tumor incidence can vary widely among species. The relative potency of carcinogens may be assessed by normalizing adduct levels for doses that induce 50% of tumors at the MTD and then considering the dose required to generate that number of adducts (Otteneder and Lutz, 1999). Adduct measurements also can estimate the occurrence of saturation pathways and where dose–response relationships become nonlinear for both adduct formation and tumor incidence. Different tumor-adduct profiles have been shown, depending on the carcinogens and the dose level (Pledger et al., 1977). Figure 12-1 summarizes different types of data for DNA-adduct levels and tumor formation (Poirier and Beland, 1992). It shows that in some cases, the relationship of adduct levels to tumor occurrence is linear, but in some cases, the slope of the effect can be different and saturation pathways occur. Thus, prediction of the effects of individual tobacco constituents in the context of other constituents is complex. It is unknown whether the cancer effect of co-exposures is synergistic or additive, but at different dose levels, either can be observed (Poirier and Beland, 1992). Extrapolation of animal studies to humans also can be strengthened by demonstrating the same occurrence of carcinogen–DNA adducts in experimental animals and humans. Unfortunately, most studies have used only single-dose or short-term exposure (Otteneder and Lutz, 1999), so it is unknown how this relates to chronic exposure. Most of these studies also investigate levels in the experimental animal liver rather than in human target organs.

Different methods are available for assessing tobacco-related cancer risk in humans. External exposure markers attempt to predict exposure without regard to interindividual differences in smoking behavior and cellular processes. Biomarker assays can assess internal exposure, the

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(Thilly, 1985). The limitations for extrapolation to animal studies are described below. Thus, *in vitro* models might be useful for suggesting which tobacco constituents should receive the highest priority in evaluating PREPs, but they cannot be used to quantitatively support such a claim.

The use of laboratory animal models can provide an estimate of the effects of PREPs. Typically, studies used for risk assessment have followed protocols established by the National Toxicology Program to prioritize compounds for study as potential human carcinogens (Boorman et al., 1994; Goldstein, 1994; Fung et al., 1995). However, these studies use maximally tolerated doses (MTDs) over the animal's lifetime. Definition of the MTD is based on a subchronic, 90-day study, in which the highest dose that does not affect overt toxicity or growth is chosen. A consideration of the various limitations of MTDs for extrapolation to low-level exposures would lead to the conclusion that risk assessments based on MTD tumor incidences can overestimate human risk (Portier et al., 1994). In trying to understand the prediction of risk based on the MTD, there is a correlation for a dose that induces tumors at 50% of the MTD (Krewski et al., 1993) and at 50–75% of the MTD (Haseman and Lockhart, 1994), but it is unclear whether this information validates the use of the MTD or suggests that even 50% dose levels still cause significant physiological perturbations. Thus, the extrapolation of animal studies to humans remains questionable for harm reduction evaluation under these experimental designs. The use of animal studies might be rational, however, if the doses approximate human levels of exposure and if the experimental animal model does not possess a sufficiently different physiological response to carcinogen exposure compared to humans. Transgenic mice are now available with human genes that may screen potentially carcinogenic agents more rapidly than the 2-year bioassay (Tennant et al., 1995), but multiple dosing protocols are needed (Schmezer et al., 1998). However, their use for harm reduction has not been considered previously, and doses affecting toxicity will be different than those for other animal models.

The use of experimental animal studies to predict cancer risk is more qualitative than quantitative for a number of reasons usually related to physiological differences and expanded protocols (Int. Panel, 1996; Sverbay, 1987). Mice and humans have many similar genetic alterations, but there are some important differences such as telomerase activity. Target organ specificity is very different under typical experimental conditions (Benigni, 1998). There are large quantitative differences in cancer risks among any organ in experimental animals. For a variety of tissue sites, including lung, liver, breast, and skin, pairs of inbred mice differ by a hundredfold in risk for tumor development. Detailed analyses of these differences using back-cross, recombinant inbred, and recombinant congenic breeding protocols have shown specific determinants for initiation, promotion, premalignant progression, and metastatic stages. There are even larger quantitative differences in cancer risk by organ among experimental animals. In most cases, susceptibility or resistance is a property of the target tissue, not of the host is susceptibility to genotoxic substances such as *N*-nitrosamines. A direct relationship between in vitro experimental studies (i.e., metabolic activation of chemicals by cytochrome P-450s), in vitro mutagenicity tests, experimental animal studies, and human epidemiology has not been proven. Although there tends to be concordance among experimental studies, this is not 100% true, and extrapolation to humans is far from concordant. For the prediction of carcinogenicity in humans, the sensitivity of experimental studies is high and the specificity is very low. Some studies suggest that consideration of multiple assays yields greater productivity (Tennant and Ashby, 1991), but only if these compounds are mutagenic (Int. Panel, 1996) (Tennant and Ashby, 1991; Gold et al., 1993; Cunningham et al., 1993; Tennant, 1993). Chemicals that are highly reactive toward DNA are commonly mutagenic; however, in experimental animals, 84% of tested carcinogens and 66% of noncar-

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that contain tobacco or tobacco constituents, a dose–response model should be developed for cancer risk that indicates risk for use by "never smokers" who initiate regular use with the PREP.

Harm reduction method in context assessment. An assessment is needed of the predicted reduction in risk versus the remaining risk of other tobacco constituents and consideration of new or altered tobacco constituents.

Individual susceptibility and population- attributable risk for successful harm reduction. Are there individual susceptibilities (e.g., age, gender, race, heritable traits, previous tobacco exposure) that can modify the success of a PREP (increased, decreased, or no change in risk), and what is the frequency of these traits in different smoker populations?

3. *Integrated harm reduction method assessment*:

Final considerations. Consideration of the above models should provide a summary statement and prediction of the numbers of cancers that are avoided due to the method. If the reduction in exposure is proposed only for carcinogens, possible effects on other tobacco-related illnesses and total mortality must be considered.

The causality assessments (linkage and reduction) can be provided in the format of Sir Austin Bradford Hill (Hill, 1964), which was originally proposed in the first Surgeon General's report[3] (Table 12-2). In the evaluation of a PREP, it must be decided which disease outcome or outcomes are to be targeted. The role for all cancers could be evaluated with this model, or perhaps only lung cancer, because the lung is the most sensitive organ to tobacco smoking. For smokeless tobacco products, oral cancers can be used. These targeted outcomes might change because new PREPs may increase risk in non-lung or non-oral cavity cancers, or though exposures to some carcinogens decrease, the risk from other tobacco product constituents (i.e., additives, fibers) might increase.

Various scientific methods are used to assess carcinogenicity and carcinogenic risk. These appear in Table 12-3, along with their strengths and limitations. Most of these methods, however. have limited use currently for harm reduction evaluations. The assessment of carcinogenicity in the laboratory is focused on identifying potential human carcinogens, and fewer data are available for effects at different doses in ranges to which humans are exposed. Also, these studies are designed to identify risks using continuous exposures, and there are few studies that consider intermittent exposures or exposures that begin at high dose and then change to low dose. These types of studies are likely more relevant to predicting the effects of PREPs.

The use of in vitro cell culture models and DNA-binding studies that focus on mutagenesis is attractive because they can provide toxicity data rapidly. Many models are available and have helped elucidate various mechanisms of carcinogenesis (Taningher et al., 1990; Balmain and Harris, 2000). Combinations of assays are traditionally used to better identify genotoxic compounds and to assess the genotoxic potential of different cigarettes (Bombick et al., 1997). Although in vitro models that provide positive results for genotoxic damage best predict carcinogenesis in experimental animal studies qualitatively or semiquantitatively (Taningher et al., 1990), mutagenicity in a cell culture is difficult to extrapolate to the in vivo models, whether animal or human (Rosenkranz and Klopman, 1993). Also, a negative result in cell culture systems is less reliable (Thilly, 1985) (Zeiger, 1987).Mutations found in the *Salmonella* assay predicted carcinogenicity in laboratory animals with an overall accuracy of 59.5% (Lee et al., 1996). However, simple concordance analysis of predicitivity (yes or no) may not be as useful as considering predictivity in relation to mechanistic pathways (Butterworth, 1990). Some limitations for dosing in cell culture studies are related to the balance between mutation and cell survival

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Smokers have learned to block filter ventilation holes, with concomitant increase in tar exposure of more than tenfold compared to the standard FTC method (Kozlowski et al., 1982). Blocking can occur with the fingers, lips, or tape, and can be intentional or unintentional.

To consider the value of a harm reduction strategy, one must consider the effects on cancer risk of the targeted reduction in exposure and then place these risks in the context of reducing exposures by any means. This process can be used for individual constituents of exposure or in the aggregate. Through this process, several predictive models should be developed that are based on adequate scientific data, not speculation. The methods listed below are used if the proposed reduction in exposure is for carcinogens. Importantly, an assessment of a PREP can only be made in the context of risk due to conventional tobacco products. Following a risk assessment model typically used by regulatory agencies, the following 3 steps are proposed:

1. Cancer linkage assessment (linking exposure to cancer)

Causality assessment. Does the compound targeted for reduced exposure cause cancer, and what do we know about the biological mechanisms for that compound? The criteria proposed in the first Surgeon General's report on smoking and health (U.S. Public Health Service, 1964), and later extended by Sir Austin Bradford Hill,[4] or their equivalents, proposed by others, should be applied, using experimental data and human experience.

Dose–response assessment. What is the dose–response relationship between targeted carcinogens and cancer risk? Where is the risk to persons from environmental tobacco smoke (ETS) within the shape of the dose–response curve? What is the optimal way to consider dose?

Causality in context assessment. How do the risks of harmful effects from the targeted compounds compare with other carcinogens in tobacco smoke? Are there data to indicate how these compounds can affect risks for former smokers or persons with ETS.

Individual susceptibility and attributable risk assessment. Are there individual susceptibilities (e.g., age, gender, race, heritable traits, prior tobacco exposure) that can modify the carcinogenic risks of these targeted compounds, and what is the frequency of these traits in different smoker populations?

2. Cancer reduction assessment (decreasing exposure to reduce cancer risk from a higher base line level):

Reduction in carcinogenicity assessment. What is the experimental evidence that reducing exposure will reverse or halt carcinogenic processes that have already begun?

Decreasing dose–response assessment. What happens to cancer risk if doses are reduced, and how much does exposure have to be reduced to result in a meaningful benefit? A model should be developed that predicts the cancer risk or rate over time for the consistent use of the harm reduction method. This model will include several scenarios in which different categories of smoking (current smoking, lifetime smoking, and age at initiation) at the time a PREP is used are studied and, for example, assume a 10, 25, 50, 75, and90% reduction in exposure. (Response is measured by a biologically effective dose, a biomarker of potential harm, or a disease outcome, not what is measured in tobacco smoke or delivered to the oral and respiratory mucosa.)

Adverse effects of harm reduction strategies. A model should be developed that predicts the numbers of individuals who begin smoking, do not quit, or resume smoking after quitting due to the availability and knowledge of a PREP, or belief that such products are safe. For new products

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1985; Melnick and Huff, 1992; Owen et al., 1987). Heterocyclic amines, are emerging as an important human carcinogen, which are formed from the pyrolysis of creatines (Knize et al., 1999). These compounds are found in smoke, and the removal of proteins from tobacco before making cigarette smoke condensate substantially reduces mutagenicity (Clapp et al., 1999).

Although it is conceivable that some harm reduction strategies might decrease exposures to PAHs, TSNAs, or aromatic amines, singly or combined, the assessment of real benefit must consider the effects of altering these carcinogens in the context of the complex exposures resulting from tobacco products (Krewski and Thomas, 1992). Thus, it is critical that PREP assessment include consideration of complex mixtures. Assays are available that can do this, as reviewed in Chapter 10. Separately, decreasing one or more tobacco constituents might not affect cancer risk if other compounds such as 1,3-butadiene, benzene, aldehydes, and acrolein are not affected, or the risks from additives or fibers might be comparatively more important. There are insufficient data to currently conclude that overall cancer rates would decrease proportionally to the reduction of a carcinogen, because although one type of cancer might decrease, others might increase. Alternatively, the substitution of one lung carcinogen for another might not allow for a sufficient benefit from harm reduction strategies.

SCIENTIFIC METHODS FOR ASSESSING HARM REDUCTION STRATEGIES

The actual exposure to tobacco mutagens is dependent on the type of cigarette and how it is smoked. Over time, manufactured cigarettes and consumer choices have changed substantially. Prior to the 1950s, most manufactured cigarettes did not have filters, but more than half of all cigarettes had filters by the beginning of the 1960s (Cummings, 1984). Although filtered cigarettes were available earlier, about the time of the first Surgeon General's report in 1964, many people began switching to filtered cigarettes (Hoffman and Hoffman, 1997; Stellman and Garfinkel, 1986). Today, more than 98% of cigarettes have filters (FTC, 2000). The so-called tar content also has declined since the 1950s, from about 37 mg to less than 15 mg. (Hoffman and Hoffman, 1997; Cummings, 1984). Most studies published through the 1980s included subjects who probably had smoked nonfiltered cigarettes in their lifetime, and this could make smoking studies from that time more difficult to interpret.

The introduction of low-tar and nicotine cigarettes was conceptualized to make cigarettes "safer," but currently available scientific data suggest that potential benefits may not have been realized for some or most persons (see discussion of lung cancer). In actuality, many persons who smoke low-tar and nicotine cigarettes compensate for lower nicotine delivery by smoking more (Benowitz et al., 1998, 1986, 1983; Ebert et al., 1983; Gritz et al., 1983. Levels of TSNAs and benzo[a]pyrene in tobacco smoke can be similar for low-and high-tar cigarettes when people oversmoke their cigarettes (Djordjevic et al., 1995, 1997). It is unknown, however, what happens to carcinogenic biologically effective doses. While switching results in a higher peak nicotine level per cigarette, there is a lesser proportional reduction in urinary mutagenicity (Benowitz et al., 1986a,b; Sorsa et al., 1984). In one study, sister chromatid exchange levels, which have not been validated as a surrogate marker for the harm, do not change when persons switch from high-to low-tar cigarettes (Djordjevic et al., 1997), but the relation of this marker to short-term and long-term exposures, half-lives, and other factors that might confound such studies is not known.

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Aromatic amines are another class of compounds present in tobacco smoke, these consist of aromatic amines and heterocyclic amines. The latter are not reviewed here. There are substantial data to implicate aryl amines and their metabolism in human carcinogenesis (Veneis and Pirastu, 1997), especially bladder cancer in occupationally exposed cohorts (e.g., dye workers) (Cartwright et al., 1982). In experimental animals, 4-aminobiphenyl (4-ABP) adduct levels increase in both liver and bladder tissues, but the rise in the bladder as a target organ is substantial and correlated with tumor incidence (Poirier and Beland, 1992). Saturation pathways might occur in female mice at lower doses than male mice, and saturation effects at higher levels of smoking has been reported in humans (Dollinger, 1998). Aromatic amines are thought to contribute to bladder carcinogenesis in smokers too, so this is an example of a tobacco carcinogen that affects an organ distant to the route of entry. Aromatic amines are initially activated by CYP1A2, which ultimately leads to the formation of nitreunium ion that then forms a DNA adduct. *N-Acetyltransferases* (NAT1 and NAT2) play an activating or detoxifying role, depending on the arylamine (Windmill et al., 1997). These compounds are metabolically activated in the liver and transported to the kidney. Upon excretion in the urine, the bladder mucosa can further activate and detoxify the conjugates. Both NAT1 and NAT2 are present in the bladder mucosa (Kloth et al., 1994; Badawi et al., 1995). Aromatic amine biomarker studies have generally focused on hemoglobin rather than DNA adducts. Levels are higher in smokers than nonsmokers, and different types of tobacco can lead to higher adduct levels (Dollinger, 1998) (Bryant et al., 1988; Carmella et al., 1990). Different types of adducts also have been detected in urinary bladder (Badawi et al., 1996; Kadlubar, 1994). (Bryant et al., 1988; Carmella et al., 1990).

Both the gaseous and the particulate phases of cigarette smoke contain free radicals (e.g., nitric oxides in the gaseous phase) that induce oxidative damage (Hoffman and Hoffman, 1997; Pryor et al., 1998). Many components of cigarette smoke can individually cause oxidative damage (Leanderson and Tagesson, 1990). Nitric oxides may act synergistically with the particulate phase to induce DNA breaks. Although free radicals cause DNA damage in experimental systems and are suspected to be involved in carcinogenesis (Floyd, 1990), a direct relationship to human carcinogenesis has been suspected but not proven (Loft, 1996) (Marnett, 2000; Poulsen et al., 1998). It is difficult to measure free radicals and oxidative damage in humans from tobacco smoke or any other source (endogenous or exogenous), because it is impossible to distinguish free radical sources and biomarker methods can artifactually induce oxidative damage (Loft, 1996) (Marnett, 2000). Among the most common methods is to measure 8-oxodeoxyguanosine, one of the most abundant products of oxidative damage and can be seen in human lung (Inoue, 1998), using high-performance liquid chromatography (HPLC) and electrochemical detection (Park et al., 1989; Helbock et al., 1998; Loft and Poulsen, 1996). Levels are generally higher in leucocytes and in the urine of smokers compared to nonsmokers (Loft et al., 1992; Asami et al., 1996). In a comparison of 100 smokers in a smoking cessation program and 82 smokers who were not quitting, the cessation group lowered urinary excretion levels of 8-oxodeoxyguanosine by 21%, while there was no effect in smokers (Prieme et al., 1998). While levels of 8-oxoguanine are elevated in smokers, so is the capacity to repair these lesions (Hull,1993) (Asami et al., 1996). Separately, free F2-isoprostanes, a marker of lipid peroxidation, were measured in the plasma of 10 smokers and 10 nonsmokers. Levels were higher in smokers than in nonsmokers and decreased with abstinence (Morrow et al., 1995).

Other constituents of tobacco smoke can also play a role in human carcinogenesis. For example, although 1,3-butadiene is present in cigarette smoke at "low" levels, it is considered a potent carcinogen in experimental animal studies, that specifically affects the lung (Huff et al.,

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Tobacco products and smoke contain *N*-nitrosamines (Fischer et al., 1990, 1989; Tricker et al., 1991; Brunneman et al., 1996), which are among the most potent rodent carcinogens (Lewis et al., 1997). Some of the *N*-nitrosamines in tobacco smoke are specific for tobacco (TSNAs), whereas others are the same types formed from dietary exposures. *N*-Nitrosamines cause cancer in more than 40 animal species, and there is target organ specificity, including for TSNAs and lung tumors (Riverson, 1989) (Lewis et al., 1997), where there is a biphasic response in experimental animals indicating both a high affinity response at lower exposure levels and a saturation effect at higher levels (Pledger et al., 1977; Belinsky et al., 1990). Experimental animal studies also show that higher doses of exposure cause tumors in less time, suggesting that intensity and duration are equally important (La and Swenberg, 1996; Lewis et al., 1997). Mutations in K-Ras have been found in lung tumors of experimentally exposed animals (Chen et al., 1993). TSNAs can transform human bronchial epithelial cells (Klein-Szanto et al., 1992). The same type of adducts that occur from TSNAs in experimental animals also have been detected in humans, including in lung tissue (Hecht, 1994). Different types of tobacco have different TSNA yields (Drunnemann et al., 1996). In humans, metabolites of TSNAs are found in urine (Hecht et al., 1994; Carmella et al., 1995), and adducts are detected in blood, so TSNAs circulate through the body, including in persons who are passively exposed (Atawodi et al., 1998; Hecht et al., 1993; Parsons et al., 1998). The elimination half-life of several TSNAs through the urine is estimated to be40–45 days (Hecht et al., 1999). There is no mutational specificity for *N*-nitrosamines in several genes studied to date, although there is a propensity for G→A guanine to adenine transitions in experimental models (Ronai et al., 1993; Chen et al., 1993; Tiano et al., 1994). *N*-Nitrosamines undergo metabolic activation by human cytochrome P-450s located in the lung, buccal mucosa, and other tissues (e.g., CYP2E1 and CYP2A6; Patten et al., 1997; Hecht, 1998; Smith et al., 1995, 1992). Ethanol induces CYP2E1 which may have implications for oropharyngeal and esophageal cancer (Garro et al., 1981; Ma et al. 1991). Cigarette smoking and exposure to other tobacco products increase endogenous nitrosation, so that there are additional exposures to nitroso compounds (Nair et al., 1996). The metabolic activation of TSNAs and other tobacco *N*-nitrosamines leads to the formation of DNA adducts in target tissues or is associated with specific cancers (Liu, 1993; La and Swenberg, 1996; Yang et al., 1990; Tiano et al., 1993; Nesnow et al., 1994; Zhang et al., 1991; Change et al., 1990). TSNAs form three different classes of DNA adducts (Hecht, 1999). The first involves methylation of different nucleotides, which also are formed by other *N*-nitrosamines, and some of these adducts are more promutagenic than others (O^6-methylguanine more readily causes mutations than N^7-methylguanine), and there are different repair enzymes for each. The O^6-methylguanine is repaired by O^6-alkyl–alkyltransferase. The activity of this enzyme varies among people and can be reduced in smokers, because once methylated it becomes inactive.[97] Other classes of adducts formed by TSNAs, which are bulky (Hecht, 1999; Atawodi et al., 1998), are probably repaired by nucleotide excision and recombination repair, similar to PAHs. The activity of these repair pathways also varies widely among individuals. Different tobacco products contain widely differing amounts of TSNAs (Fishcer et al., 1989), Snuff use can lead to higher levels of TSNs than smoking (Hecht et al., 1994), and changing smoking patterns can result in higher delivery of TSNAs.[98] For example, Swedish snuff products contain substantially fewer TSNAs than snuff sold in the United States. Lower-tar and nicotine cigarettes result in greater exposure to TSNAs than high-tar and nicotine cigarettes (Hoffman and Hoffman, 1997; Brunnemann et al., 1996). The third type of DNA adducts formed from TSNAs is related to oxidative damage (Hecht, 1999).

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many chemicals and classes,) has received insufficient attention, and exposure to tobacco constituents as complex mixtures would provide the most compelling evidence for prediction of a successful PREP. Cigarette smoke condensate is mutagenic in bacterial and human cell lines (Matsukura et al., 1991) and can cause a malignant transformation in human bronchial epithelial cells (Klein-Szanto et al., 1992). Whole smoke, which is also mutagenic, can be used as well (Bombick et al., 1997). Both the vapor phase of ETS and unfiltered ETS exposure causes lung cancer in experimental animals (Witschi et al., 1997). There is some evidence to suggest that the mutational spectra of a complex mixture reflects mostly that of the dominant chemicals in the mixture (DeMarini, 1998), although experimental animal studies of DNA adducts from benzo[a]pyrene and coal tars indicate that total adduct levels are not related to BP content alone (Goldstein et al., 1998), suggesting that studying single chemicals is not sufficient to represent the effects of complex mixtures. Further, various polycyclic aromatic hydrocarbons cause different hotspots in p53 (Smith et al., 2000), and different dose levels of complex mixtures might have additive or synergistic effects (Poirier and Beland, 1992; Hecht et al., 1999) Thus, more studies are needed to determine the best approaches to assessing the mutagenicity and carcinogenicity of complex mixtures (Guengerich, 2000).

Several constituents of tobacco are considered likely agents of human carcinogenesis. Some of these are reviewed here to highlight the considerations needed in considering harm reduction strategies.

People are commonly exposed to PAHs through tobacco products, diet, occupation, and consumption of fossil fuels (i.e., burning coal or wood). These compounds are formed from the incomplete pyrolysis of tobacco leaves, and many types of PAHs are present in tobacco smoke as a complex mixture. Parent PAHs can be detected in human lung tissue (Seto et al., 1993; Lodovici et al., 1998). It is estimated that smokers are exposed to 2–5μg of PAHs per day per pack of cigarettes, and our diet provides of PAHs 3μg per day (Hoffman and Hoffman, 1997; Lioy and Greenberg, 1990; Waldman et al., 1991). As a class, they are mutagenic and carcinogenic in organs of experimental animals (including the lung) and humans (IARC, 1986; Van Delft et al., 1998; Hoffman and Hoffman, 1997). PAHs have different potencies, which are thought to be related to metabolic activation of a compound that leads to either a bay region.
diol–epoxide (potent) or a fjord region diol–epoxide (nonpotent) compound. PAHs are metabolically activated in humans through *CYP1A1*, *CYP1B1*, and *CYP3A4(Shimada et al., 1996; Kim et al., 1998)*. They are conjugated for excretion by glutathione *S*-transferases, sulfuronyl transferases, and glucuronyl transferases (Robertson et al., 1988), and the lack of such activity increases mutagenic potential (Romert et al., 1989). In experimental animals treated with benzo[a]pyrene, the half-life of DNA adducts following a single dose is 15 days in the liver, 17 days in peripheral blood lymphocytes, and 22 days in lung (Ross et al., 1990). In humans, there is more than a hundredfold variation in the resultant capacity for DNA-adduct formation (Harris et al., 1974) due to variation in induction and activity for these activating and detoxifying enzymes. PAH-related DNA adducts have been demonstrated in human lung (Luzick, 1990; Kato et al., 199), while the presence of hemoglobin and albumin adducts also shows that these compounds circulate in human blood (Day et al., 1990; Kriek et al., 1998). In vitro studies indicate that PAHs can cause the same types of p53 mutations observed in human tumors (Smith et al., 2000; Denissenko et al., 1996). DNA damage from PAHs is repaired by both excision and recombination pathways, and while there is clearly interindividual variation in the DNA repair capacity of these pathways, such variation have received little attention for PAHs (Xu et al., 1998).

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numerous carcinogens in tobacco, which cause many types of DNA damage. New microarray technologies will provide sequence data for many genes, RNA expression profiles or protein expression profiles that—with sufficient bioinformatic support—a characteristic profile could enable of tobacco effects to be discerned.

Tobacco smoke exposes the entire respiratory and upper gastrointestinal mucosa to carcinogens, whereas smokeless tobacco exposes only the oral cavity and the gastrointestinal mucosa. Thus, these entire "fields" are at risk for the development of preneoplastic and neoplastic lesions (Slaughter et al., 1953; Strong et al., 1984). A field effect for cancer has been demonstrated on a molecular basis, where different molecular lesions were found in persons with multiple synchronous lesions (Sozzi et al., 1995).

TOBACCO MUTAGENS AND CARCINOGENS

The use of tobacco products, as they are intended to be used, results in exposure to more than 100 mutagens and carcinogens (Hoffman and Hoffman,1997; Zaridze et al., 1991) that have different potencies and effects. Mainstream smoke consists of particulate and vapor phases. Although carcinogens have been identified in both the vapor and the particulate phase, the latter shows more overall carcinogenic activity. The particulate phase contains more than 3,500 compounds, of which at least 55 have been identified as possible human carcinogens (Hoffman and Hoffman, 1997). The vapor phase contains more than 500 compounds (Hoffman and Hoffman, 1997). A list of some of these constituents is provided in Table 12-1, which is not all inclusive.

Tobacco mutagens and carcinogens have different potencies and target organ specificities. A recent critical review summarizing data for tobacco constituents proposed that tobacco-specific nitrosamines (TSNAs) and polycyclic aromatic hydrocarbons (PAHs) are classes of compounds that most affect human cancer risk.[9] Although this may be true, it is currently difficult to prove in human cancer, especially because these exposures are mixed with others. Other compounds also are likely to be important. The existing data are not sufficient to determine whether some compounds are clearly more carcinogenic in humans than others when delivered through the use of tobacco products, and whether there is a synergistic effect of coexposure. Therefore, the assessment of a harm reduction strategy for cancer must consider these constituents individually and as part of a complex mixture since the former can provide mechanistic information but only the latter can be used to fully understand the effect of PREPs on carcinogenesis.

Tobacco and tobacco products have changed over time, with resultant differences in predicted exposure using the Federal Trade Commission (FTC) method for the measurement of "tar" and "nicotine" (Hoffman and Hoffman, 1997). It is known that the FTC method for estimating tar exposure underestimates actual human exposure because it does not sufficiently mimic human smoking behavior (Hoffman and Hoffman, 1997). Specifically, using a protocol that mimics actual human smoking behavior shows that the FTC method substantially underestimates the exposure to TSNAs and benzo[a]pyrene [BaP] (Djordjevic et al., 2000). While smokers of low-nicotine cigarettes have somewhat lower delivered levels of BaP and TSNAs, the daily amount of tar delivered is similar (Djordjevic et al., 2000). Therefore, in this report so-called tar yields do not imply actual tar to exposure.

Although it is important to understand the differences in risks by chemical class, in order to assess PREPs, it must be realized that affecting the exposure to one compound or class might not account for similar proportional decreases of other compounds, and we do not know if removing one compound or even a whole class will reduce unless other classes of compounds are also decreased. Further, the study of mixtures (i.e., the real-life scenario of simultaneous exposure to

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oncogenes, only one allele has to be activated, whereas for tumor suppressor genes, both alleles are usually inactivated. Thus, the former is a dominant trait, while the latter is recessive.

Oncogenes occur when proto-oncogenes, responsible for normal cellular processes, are mutated. Multiple oncogenes are involved in the pathogenesis of solid tumors including lung cancer (Kohno and Yokota, 1999; Fong et al., 1999; Rom et al., 2000). Only a few oncogenes, such as K-ras and c-MYC have been identified as playing crucial roles in the pathogenesis of several tobacco-related tumors (Reynolds et al., 1991; Rodenhuis et al., 1987; Slebos et al., 1988). However, most oncogenes remain to be discovered. The ras gene family consists of three members (K, N, and H). They are membrane-bound proteins that bind to guanosine 5'-triphosphate (GTP) when activated, and to guanosine 5-diphosphate (GDP) when inactivated. Activation sends a signal to the nucleus, via a cascade of kinases, that eventually results in the activation of transcription factors. Activating ras mutations occur at codons 12, 13, and 61 and result in loss of intrinsic guanosine triphosphates (GTPase) activity, locking in the activated form (Bos, 1988), experimental studies support the role of tobacco carcinogens that affect ras in lung cancers (Ronai et al., 1993). It has been reported that ras mutations are present usually only in smoke-related lung cancers (Gealy, 1999) (Slebos et al., 1991). Such mutations also can be observed in smokers without lung cancer, suggesting that they can be early markers of smoking-related damage (Slebos et al., 1991; Lehman et al., 1996; Yakubovskaya et al., 1995; Scott et al., 1997).

Tumor suppressor genes in tobacco-related cancers include p53 (also known as TP53), $p16^{INK4A}$ (p16), retinoblastoma (RB), and fragile histidine triad (FHIT) genes. A frequent method of inactivation of one allele of recessive oncogenes is by allelic deletion (i.e. loss of DNA material on one of the alleles). Often, this deletion is extensive and involves not only the gene of interest, but adjacent genes as well. The p53 gene is a tumor suppressor gene, and mutations of this gene may represent the most common genetic abnormality discovered to date in tumors, being present in about 50% of human carcinomas (Hollstein et al., 1996). It plays a central role in the balance between gene transcription, cell proliferation, and apoptosis. DNA damage results in the induction of genes upstream of p53 (Oren, 1999), which then stimulates p53 induction and stability through posttranslational modifications. This in turn affects *p21, MDM2, GADD45, BAX,* and other genes responsible for DNA repair, and delay of the cell cycle to allow additional time for DNA repair, or triggers cell death when DNA repair is not possible. The (p16) gene is located on chromosome 9p, and its protein plays a crucial role (along with the retinoblastoma gene product and the cyclins) in regulating the cell cycle. It is inactivated in many smoking-related cancers including non-small-cell lung, head and neck, and pancreatic cancer and squamous carcinomas of the esophagus (Geradts et al., 1999; Liu et al., 1995; Lydiatt et al., 1995), and occasionally bladder tumors (Orlow et al., 1999). Inactivation occurs by many mechanisms including hemizygous or homozygous deletions, point mutations, or aberrant methylation of the promoter region. The latter is an example of tobacco smoke constituents affecting genetic function without causing a mutation (i.e., an epigenetic change) (Belinsky et al., 1998). The FHIT gene is a putative tumor suppressor gene located on chromosome 3p14 (Sozzi et al., 1998). Inactivation of the gene product has been described in many tumors including lung, head and neck, and esophagus.

It might be possible to consider mutations in different genes as "molecular fingerprints" of causation by tobacco smoke for an individual. This could be helpful in considering the effects of different types of tobacco products and changes in tobacco constituents over time. It might also be possible to identify which tumors in an individual were caused by tobacco versus some other agent. However, no such "fingerprints" have been identified for tobacco smoking, although some types of lesions occur more frequently (Kondo, 1996; Taheshima, 1993). This may be due to the

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of DNA damage and DNA repair (Loebab, 2000). Individual adducts may be repaired by excision repair pathways, while chromosomal aberrations are repaired by recombination repair pathways. In addition to DNA repair, other protective mechanisms can reduce the harmful effects of DNA damage, such as lengthening the G1 or G2 checkpoints to allow more time for DNA repair or triggering cell death (apoptosis). Unfortunately, some mutations might block the entry into these checkpoints or evade cell death processes. In addition to repair pathways that remove adducts, there are other control methods if these mechanisms or pathways fail. There are DNA repair enzymes that recognize and repair mismatch damage, and if this does not occur, cell death may be triggered. The combination of repair and cell turnover leads to a half-life of carcinogen–DNA adducts. To date, the effects of chemicals on these repair and control pathway, and interindividual differences in DNA repair, cell-cycle control, and cell death have only recently some attention (Sumida et al., 1998).

The relationship between a mutagen and mutation is complex and may depend on the dose of the mutagen (Van Delft et al., 1998; La and Swenberg 1996). Low-dose exposures are often difficult to evaluate in vitro or in vivo because of mutational background rates, and extrapolation of mutation rates from high-dose to low-dose exposures depends on assumptions that may not be true (Liber et al., 1985). Mutation rates for exposures that switch from high dose to low dose and how the mutational spectra changes have not been studied.

In summary, for a tobacco constituent to cause a DNA lesion that confers a selective clonal advantage on a cell that ultimately becomes cancerous, the constituent must be absorbed and metabolically activated; it has to damage DNA, which evades repair; it has to occur in a critical part of a critical gene; and finally, the cell must evade cell death. Moreover, this has to occur in the target organ. Internal exposure can be affected by smoking behavior or storage depots in the body (e.g., adipose tissue). These pathways are important to consider for harm reduction strategies because altering the levels of different tobacco constituents or complex mixtures might affect these pathways differently, so that the net effect on carcinogenicity may not be predictable **a priori**, either for an individual or for the population.

CARCINOGENESIS

Carcinogenesis is a multistage process involving many different genes (Devereux et al., 1999). (DNA damage is necessary, but not sufficient, to cause tumors as evidenced in experimental models (Pledger et al., 1977). One conceptual approach to understanding carcinogenesis is to consider that cancer is driven by defects in either caretaker, gatekeeper, or landscaper genes (Kinzler and Vogelstein, 1997, 1998). Caretaker genes are those responsible for maintaining genomic integrity, such as DNA repair and metabolism. Mutations or inherited variants in these genes increase the risk of mutations in other genes. Gatekeeper genes are those involved in controlling cell cycle, and replication of the genome, triggering apoptosis, and assisting caretaker genes in maintaining genomic integrity. Mutations in gatekeeper genes increase the risk for a cell to replicate uncontrollably and increase the likelihood of permanently establishing mutations. Landscaper genes are those that affect the external environment around the cells and thus control adjacent cells. Current data do not exist to indicate that tobacco-related harm preferentially affects any classes of genes, but an effect of tobacco carcinogens on all classes of genes is plausible and suggested by the observed complex genetic alterations in lung and other cancers.

Another way to classify cancer genes is to consider them as oncogenes or tumor suppressor genes. This classification is based on studies showing that overexpression or mutation of the former increases proliferative potential, while loss of the latter stimulates proliferative potential. For

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cation, deletion). The genetic damage follows a failure of several protective mechanisms. The first line of defense against chemical insult involves metabolizing enzymes that are intended to aid excretion of potentially damaging chemicals in the body (produced endogenously or coming from exogenous sources) (Guengerich, 2000). For tobacco constituents, this "excretory" process gone wrong is a multistep pathway simplistically described as (1) entry of the mutagen into the body (i.e., oral, respiratory, and gastrointestinal mucosa) and its distribution throughout the body; followed by (2) recognition by an organ that this is a foreign substance in need of excretion (e.g., lung, liver, bladder); (3) use of enzymes for metabolic conversion of the chemical so that it can be bound to an excretory conjugate (Guengerich, 2000);(4) binding to DNA rather than an excretory conjugate; and (5) formation of a DNA adduct or a lesion that then results in DNA damage. A mutagen might be made more water soluble or able to bind an excretory conjugate (e.g., glutathione) through several chemical reactions catalyzed by cytochrome P-450 (CYP) and other enzymes, followed by conjugation catalyzed by enzymes (e.g., glutathione *S*-transferases, glucuronyl transferases, sulfuronyl transferases). Every one of these steps can influence cancer risk (Perera, 1997; Hecht, 1999; Van Delft et al., 1998), where greater activity increases the risk of DNA damage, while greater conjugation and excretory capacity could reduce risk. Metabolic conversion and conjugate binding is a complex pathway that differs for different classes of mutagens, and there are redundant pathways (Guengerich, 2000; Nakajima et al., 1995; Anttila et al., 1992; Grundy et al., 1998; Brennan, 1998; Anttila et al., 1993, 1995). Different parts of an organ such as the lung may have different capacities for activation and detoxification (Bartsch, 1991; Gereste, 1991; Shimada, 1996; Rojas, 1992; Anttila et al., 1993; Petruzzelli et al., 1989). Enzymes that are responsible for metabolic activation and detoxification can be induced by exposures, which could further affect the level of subsequent DNA damage (Gurengerich, 2000; Nakajima et al., 1995; Bartsch et al., 1995; Ciruzzi et al., 1998; McLemore e al., 1990). Thus, when manipulating the levels of carcinogens in tobacco products, it is important to consider how these changes might affect any of the above steps. Separately, it is well known that people have different heritable abilities for these steps, so manipulating the level of one or more tobacco product constituents might affect people differently.

If a mutagen binds to DNA, additional processes must fail before a mutagenic event occurs, and this takes place more often for some mutagens than for others. Thus, not all mutagens are human carcinogens. One form of DNA damage is a DNA-adduct, which is a nucleotide with a chemically bound mutagen or some part of the mutagen. There may be some specificity for the sites of DNA adducts to occur within the genome, but adducts can form anywhere in the genome (La and Swenberg, 1996). Importantly, for the DNA adduct to contribute to the carcinogenic process, it must lead to a mutation and that mutation has to occur in a critical part of a critical gene.

Chemicals within the same class can have different capacities to form reactive intermediates and cause DNA-adduct formation in different parts of a gene. Therefore, simply altering the levels of a specific class in a harm reduction strategy might not affect the important chemical within that class, and the formation of a new adduct due to changes in chemical constituents might result in greater degrees of mutagenicity.

The chemical binding to DNA through the formation of adducts, for example, can lead to nucleotide sequence changes (insertions, deletions, or substitutions). It also can lead to gross chromosomal aberrations such as breaks, deletions, or translocations. These events occur when the mutagen causes errors during DNA replication or mitosis. However, there are protective mechanisms should any of these types of DNA damage occur, and cancer develop due to the imbalance

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Cancer

Around 1950, Doll and Hill (Doll and Hill, 1950), Wynder and Graham (Wynder and Graham, 1950), and others reported the extremely high incidence of smoking in lung cancer patients. In fact, lung cancer was a rare disease before smoking (Doll and Hill, 1950). If one employs almost any method to assess causality, such as that proposed in the first Surgeon General's report on smoking (Public Health Service, 1964) and later articulated in more detail by Sir Austin Bradford Hill (Hill, 1965), then clearly the use of tobacco products causes cancer. This conclusion comes from substantial epidemiology, laboratory animal, and in vitro studies. Tobacco smoke contains more than 100 carcinogens and mutagens, many of which are classified as carcinogens based upon human and animal studies (IARC, 1986), the latter include lung tumors in the same organs as cancers occur in humans. It is estimated that 20% of all cancers worldwide are attributable to smoking (Parkin et al., 1999).

If a regular smoker successfully quits, then the risk of cancer decreases, but the risk of cancer in former smokers does not decrease to the level of "never smokers". Thus, the concept of harm reduction by reducing exposure to tobacco carcinogens might be plausible if the exposure is significantly reduced, but the reduction in risk could not be more than that for a former smoker and would probably be less. Therefore, the most beneficial harm reduction strategy in smokers is to stop smoking.

The assessment of cancer risk from potential reduced-exposure agents (PREPs) must consider mechanisms of mutagenesis and carcinogenesis. This chapter will focus on only four types of cancer caused by cigarettes and tobacco-containing products, although smoking causes other cancers as well (Doll et al., 1996); two of these are examples of the most common cancers related to tobacco (lung and oropharyngeal), and one is an example of a cancer that occurs remotely from the site of entry of the carcinogen into the body (bladder). The fourth cancer is one in which tobacco is believed to reduce risk (endometrial). In this chapter, a mutagen is defined as a compound that causes DNA damage of any sort. A carcinogen is defined as a compound that contributes to cancer, independent of the mechanism. A tobacco constituent is any compound from a tobacco-containing product, used in an intended or unintended fashion, which results in human exposure.

MUTAGENESIS AND DNA DAMAGE

Cancers result from an accumulated amount of mutations (changes in nucleotide sequence) or gross chromosomal damage. There are several pathways to such DNA damage. Genetic damage occurs because a mutagen, or its activated metabolite, binds to or otherwise interacts with DNA. This mutagen can then cause a promutagenic lesion or in some other way perturb the genetic structure resulting in a gross chromosomal alteration (aneuploidy, break, translocation, amplifi-

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